Table 1
Clinicopathologic characteristics of the patients and tumors ($n = 302$).

	Number	%
Mean age, years (range)	56.4 (27–86)	
Menopausal status		
Premenopausal	109	36.1
Postmenopausal	193	63.9
Tumor laterality		
Right	166	55.0
Left	136	45.0
Tumor location		
Upper inner quadrant	90	29.8
Lower inner quadrant	40	13.2
Upper outer quadrant	126	41.7
Lower outer quadrant	42	13.9
Central	4	1.3
T stage		
Tis	39	12.9
T1	145	48.0
T2	109	36.1
T3	9	3.0
Tumor histology		
DCIS	39	12.9
Invasive ductal carcinoma	243	80.5
Invasive lobular carcinoma	16	5.3
Other	4	1.3

SD, standard deviation; and DCIS, ductal carcinoma in situ.

of the nodes, SLNs were confirmed whether they were stained by dye and were measured the radioactivity *ex vivo*. SLNs were numbered in order of RI count and the ratio of each node to the hottest node was calculated. All nodes with 10% or more of the *ex vivo* count of the hottest node were evaluated intraoperatively by frozen section. If metastases were identified in the SLNs, ALND was performed. In this study, patients with isolated tumor cells were considered to have SLN metastasis for which ALND was performed. ALND was omitted for patients without metastatic nodes.

Pathological examination

For frozen sections, the SLN was sectioned in the center. After the intraoperative frozen section, all nodes were submitted for permanent sectioning. The SLN was sectioned as close to 2–3 mm as possible, and processed with hematoxylin and eosin staining and immunohistochemistry using anti-cytokeratin antibodies (CAM 5.2 and AE1:AE3). Patients with metastases detected by either method were considered to be positive. If the metastatic lesion was between 0.2 and 2.0 mm in size, the node was defined as having micrometastasis. Macrometastasis was defined as a lymph node with metastatic lesions over 2.0 mm. Isolated tumor cells were defined as a lymph node with metastatic lesions less than 0.2 mm.

For comparison of categorical variables, the chi-square test was used. A p-value of 0.05 was considered statistically significant. All data were analyzed using SPSS software (SPSS Inc., Chicago, IL).

Results

In this study, SLN was successfully identified in all patients. More than one SLN was identified in 239/302 (82.5%) patients. The mean number of SLNs excised was 2.6 (range, 1–6). There were 84 patients with positive SLNs (27.8%) and 59 patients with only one positive SLN. The mean number of positive SLNs was 1.3 (range, 1–4). Total number of positive SLNs was 105. The number of positive node detected by RI and dye was 79 (75.2%). The rest was detected by RI or dye only and 24 (22.9%) were not stained and 2 (1.0%) were not detected by RI (Table 2). Table 3 shows the relationship between histological diagnosis and the order of RI count.

Table 2
The procedures of operation and the results of sentinel lymph node biopsy.

	Number	%
Surgery		
Total mastectomy	130	43.0
Lumpectomy	172	57.0
Total number of SLNs excised	782	
Mean number of SLNs excised (range)	2.6 (1–6)	
Number of positive SLNs	84	27.8
One positive SLN only	59	19.5
Total number of positive SLNs	105	
RI and dye	79	75.2
RI only	24	22.9
Dye only	2	1.0
Mean number of positive SLNs (range)	1.3 (1–4)	

SLN, sentinel lymph node; and RI, radioisotope.

Of the 105 total histological positive SLNs, 71 (67.6%) were the hottest node. All metastatic nodes were covered to the fifth degree of RI count. The most radioactive positive node of each patient was diagnosed up to the third hottest node (Fig. 1). Isolated tumor cells were only found in the hottest node. For each patient, the percentage of each node's RI count to the hottest node was calculated. When a RI count of 10% of hottest node is used as the cut-off, the proportion of positive patients captured by SNB was 94.1% and the false-negative rate was 5.9% (Fig. 2). All the hottest positive nodes were stained by indigo carmine. There was no complication associated with SNB.

Discussion

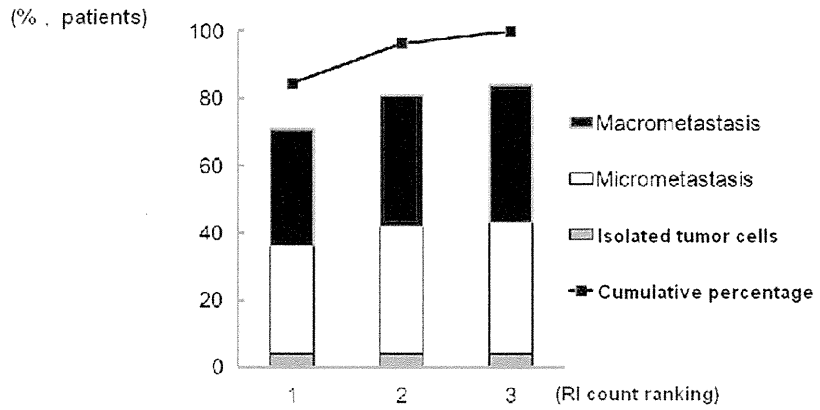
In the surgery for breast cancer patients, the theory of SLN has been established and since its introduction, SNB has allowed patients with negative biopsies to skip ALND and its associated morbidities. Though the procedure of SNB has been standardized by surgical oncologists, the ideal number of nodes to excise remains a question. In these stopping rules, patent blue or isosulfan blue was used. Instead of patent blue and isosulfan blue, indigo carmine has been used and can be used for SNB safety in Japan. This study investigated the ideal number of nodes to excise which satisfy a low false-negative rate under the use of indigo carmine blue dye.

Indigo carmine is the diagnostic dye and has been used for renal function test. Its molecular mass is 466.4 and near patent blue and isosulfan blue. Although Albo et al. and Montgomery et al. reported that anaphylactic reaction for isosulfan blue was appeared in 1.1–1.6% of patients,[8,9] there was no report of serious side effect with indigo carmine.

In this study, all positive nodes were captured up to the fifth rank in radioactivity, and the most radioactive positive node was captured up to the third rank in radioactivity. The optimal number of excised nodes was reported by some authors. McCarter et al. reported that 99.1% of patients were captured positive node up to the fourth site.[3] Almost all other studies reported that the only positive SLN is rarely identified beyond the fourth sampled node.[5] Since metastasis can be found in the 3–5th most radioactive SLN,

Table 3
Histological diagnosis of all sentinel lymph nodes in order of decreasing radioisotope count.

	1st	2nd	3rd	4th	5th
Isolated tumor cells ($n = 4$)	4	0	0	0	0
Micrometastasis ($n = 42$)	32	7	2	1	0
Macrometastasis ($n = 59$)	35	14	5	3	2
Total	71	21	7	4	2



	1	2	3
Isolated tumor cells (n=4)	4	4	4
Micrometastasis (n=39)	32	38	39
Macrometastasis (n=41)	35	39	41
Total	71	81	84
Cumulative percentage (%)	84.5	96.4	100

Fig. 1. In patient with positive node ($n = 84$), the most radioactive positive node was within third rank of radioisotope count.

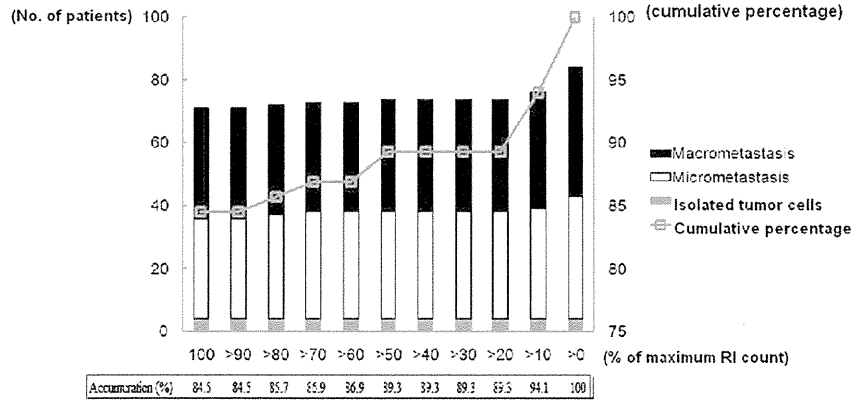


Fig. 2. Histological diagnosis according to percentage of the maximum radioisotope count.

and the TNM classification requires 6 or more lymph nodes to be excised for pN staging, the boundary between SNB and ALND can be defined at the number 6. Another guideline known as the '10% rule' was introduced in 2000 by Martin et al.[4] According to this rule, any node with 10% or more of the *ex vivo* RI count of the hottest node should be removed as a SLN. When the '10% rule' was used in this study, the false-negative rate was 5.9% and slightly high. The reported false-negative rates were 1.7% in Chung et al. [6] and 5.8% in Martin et al.[4] The accepted false-negative rate for SNB was 5%[7] and a record of less than 5% false-negatives at our institute since the introduction of SNB in 2000.

Although 22.9% of positive nodes were not stained but detected by RI only, all the hottest positive nodes were stained by indigo carmine. According to the current procedure of SNB, all the nodes that were stained and/or react to the gamma probe were excised by surgeon. Therefore the number of excised node by RI was apt to larger. And dye method is inferior to RI or combination method in detective rate, generally.[10,11] However, Narui et al. reported that a 4 node sampling method using only patent blue was reliable,[12] and in our study 2 nodes were found only through the dye method not due to accumulate RI. Metastatic disease can injure the lymphatic system and technical errors can occur during SNB. Recognition of the method's limitations and careful intraoperative palpitation are necessary.

In summary, the validity of these stopping rules in SNB under the use of indigo carmine blue dye was analyzed. Though the '10% rule' resulted in slightly high false-negative rate with the RI count method, a positive sentinel lymph node was identified in 100% of cases within the first 3 sentinel nodes when indigo carmine and RI was used. Under the use of indigo carmine, terminating SNB at 3 sampled nodes was the validity procedure to minimize the false-negative and complication rates.

Conflict of interest statement

None declared.

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

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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.

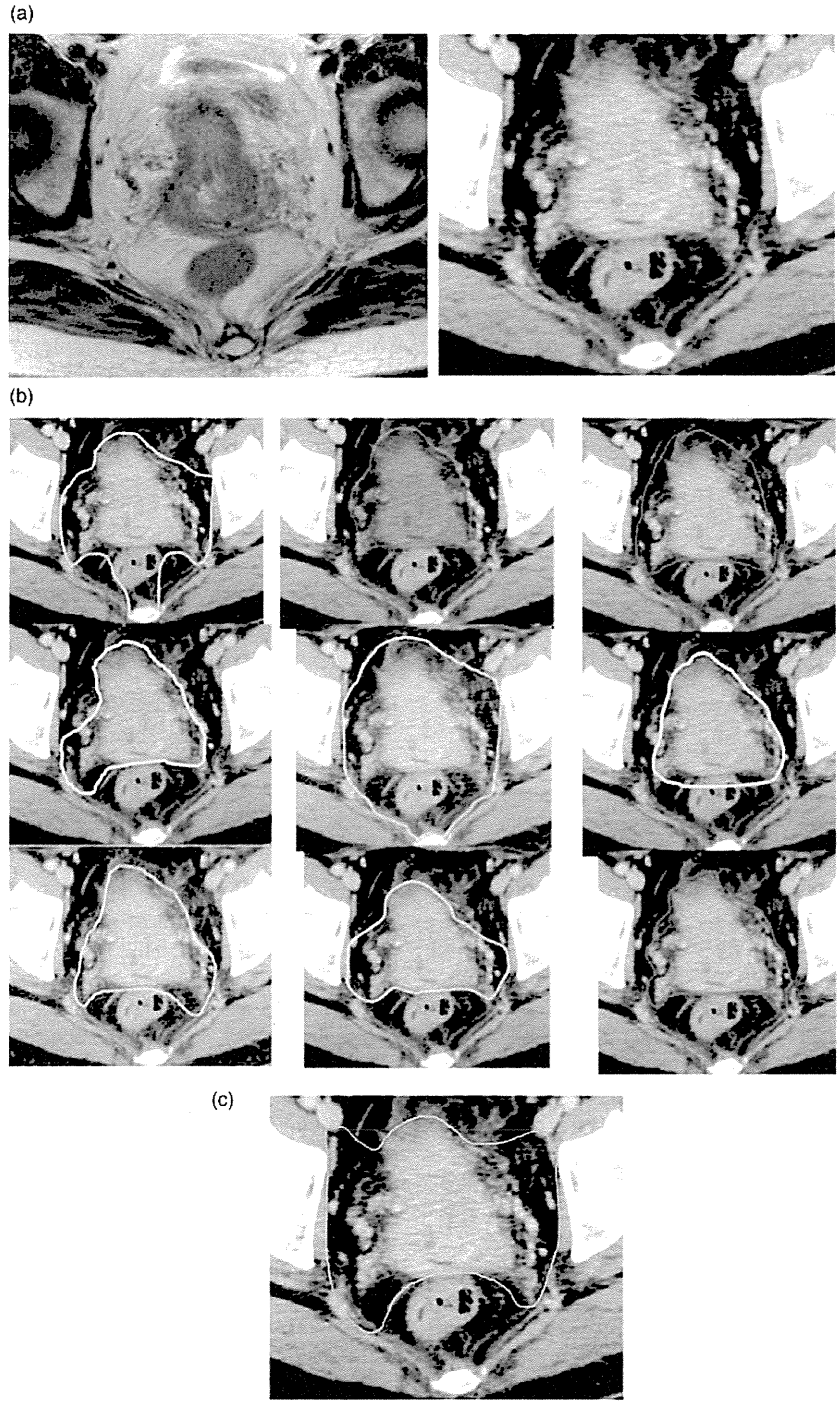

Figure 1. (a) Magnetic resonance imaging (MRI) and computed tomographic (CT) slices of a FIGO Stage IIIB cervical cancer patient who demonstrated bilateral parametrial invasion with nodular fixation to the right pelvic wall on pelvic exam. Clinical information for this patient was also distributed to 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

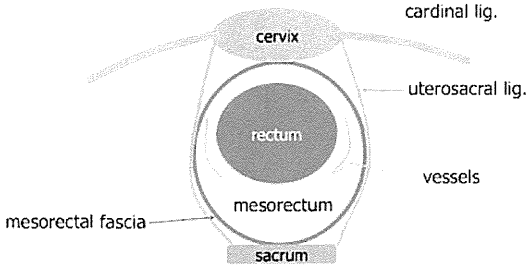

Figure 2. An illustration of the anatomical components around the cervix with reference to the parametrium.

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,

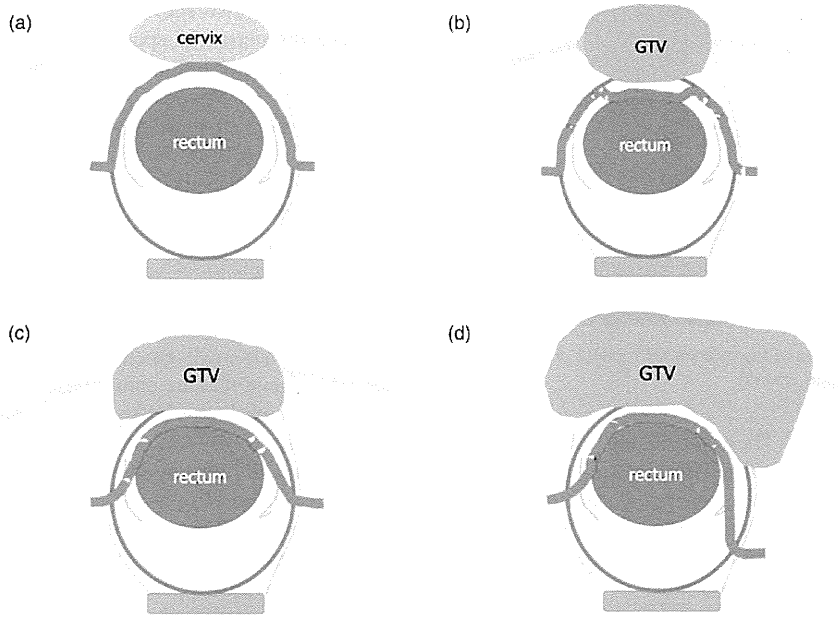

Figure 3. Stage-specific delineation schemes for the posterior border of the parametrium (solid red line). (a) Non-bulky early-stage (IB1 or IIA1) disease. (b) Bulky early-stage (IB2 or IIA2) disease. (c) Stage IIB disease (slight parametrial involvement). (d) Stage IIIB disease (massive parametrial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

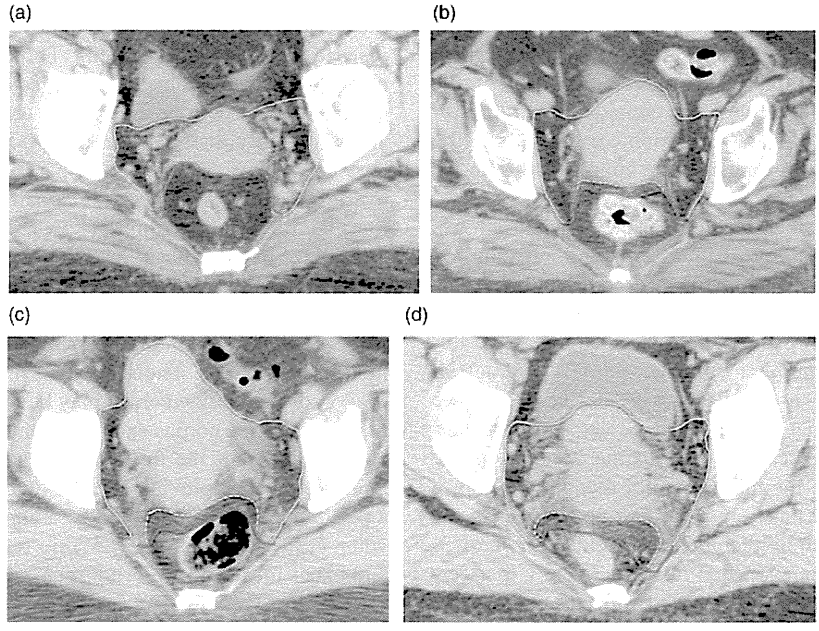

Figure 4. Actual delineations of the primary CTV (solid orange line) and posterior border of the parametrium (solid red line) according to disease status Dotted orange lines indicate the anterior border of the perirectum. (a) A case with non-bulky Stage IB1 disease. (b) A case with bulky Stage IB2 disease. (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

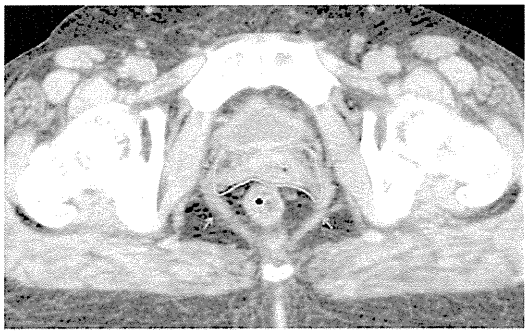

Figure 5. An actual delineation of the primary CTV (solid orange line) at the level of the levator ani (blue arrows).

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.

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Conflict of interest statement

None declared.

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Appendix

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Regular Paper

Low-dose-rate Interstitial Brachytherapy Preserves Good Quality of Life in Buccal Mucosa Cancer Patients

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Buccal mucosa cancer/Brachytherapy/^{198}Au grain/QOL.

Purpose: To determine the results and long-term changes in radiation toxicity of stage I-II buccal mucosa cancer patients treated by low-dose-rate (LDR) brachytherapy with ^{198}Au grains. Materials and Methods: A total of 133 stage I-II buccal mucosa carcinomas patients received ^{198}Au grain implantation brachytherapy between January 1982 and July 2005: 75 of them were treated by ^{198}Au grain implantation alone and 58 were treated by ^{198}Au implantation in combination with external irradiation. The average ^{198}Au-grain dose was 70 Gy in 7 days. Gross tumor areas ranged from 2.4 cm^2 to 9 cm^2, and the clinical target areas ranged from 6 cm^2 to 15 cm^2. Results: The follow-up periods ranged from 3 months to 20 years (mean: 5 years 11 months and median: 5 years 1 months). Failure at the site of the primary lesion occurred in 17 patients. Post-treatment mucosal ulceration developed in 15 patients, and all were cured within 25 months by conservative treatment. Osteoradionecrosis was diagnosed in 8 patients, but only one patient required surgical treatment. No severe complications or aggravation of complications developed more than 10 years after treatment. Conclusions: The results of low-dose-rate (LDR)-brachytherapy (BT) alone and LDR-BT in combination with external irradiation at a total dose of 25 Gy were acceptable from the standpoint of cure rate and QOL.

INTRODUCTION

Whether surgical or non-surgical, the treatment of head-and-neck cancer always involves a risk of regional discomfort and dysfunction that may affect basic life functions, including speech, chewing, swallowing, social interaction, and respiration1. Although the results of treatment strategies are usually expressed in terms of disease-free survival or overall survival, quality of life (QOL) has increasingly been used as an outcome parameter, and it is seriously considered when any treatment is selected.[2–7] "QOL" appears to have become a keyword in cancer treatment and in an increasing number of articles over the past 10 years; however, only a few studies have focused on oral cancer.[6,7] Most studies have assessed head and neck cancers as a whole, even though they are a heterogeneous group having different features depending on the site in the head and neck.[1–4,8–11]

The pathophysiological mechanisms of acute and late reactions to ionizing radiation are better understood today, but interactions between other treatment modalities and radiation therapy require constant monitoring for untoward sequelae.[12] The work of Stone provides a classic example of unanticipated late effects of irradiation with fast neutron.[13] The acute reactions were moderate and tolerable, but the late sequelae were so severe that there was little interest in pursuing treatment with fast neutrons for nearly three decades.[13] Long follow-up periods are also required to assess the effects of X-ray radiotherapy alone or in combination with surgical resection, chemotherapeutic drugs, and hormones. The late effects in normal tissues often cannot be predicted on the basis of the acute reactions, but there has been full documentation of a slow and progressive increase in the severity of late tissue and organ damage.[12]

Because low-dose-rate interstitial brachytherapy (LDR-BT) delivers a high radiation dose to only a limited volume of tissue and spares the surrounding normal tissue, it is very effective as a local treatment for early oral cancer and yields results comparable to those obtained by surgery.[14–17] Moreover, LDR-BT has long been demonstrated to be superior to surgery in terms of preservation of structure and function and a lower incidence of complications.[14–19] However, there have been no reports of studies that have focused on long-term results in terms of QOL and late complications of brachytherapy (BT).

The purpose of this study was to determine the results and the long-term changes in radiation toxicity of stage I-II buc-

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cal mucosa cancer patients treated by LDR-BT with ^{198}Au-grain.

MATERIALS AND METHODS

Study population

Between January 1982 and July 2005, a total of 133 stage I-II buccal mucosa carcinomas patients were treated in the Department of Radiation Oncology of Tokyo Medical and Dental University Hospital. T-size measured by clinical examination and N-stage was diagnosed by CT as well as clinical examination. All of the patients during that period who met the following criteria were included in this retrospective study: (1) untreated T1 or T2 squamous cell carcinoma of the buccal mucosa, (2) no cervical lymph node nor distant metastasis, (3) treated by ^{198}Au-grain BT with or without external beam radiotherapy (EBRT). Of the 133 patients who met these criteria, 75 were male and 58 were female. The median age of the subjects was 68 years, and their age range was 43 years to 87 years. According to the sub-site of the buccal mucosa, 77 patients had cancer of the proper buccal mucosa, 23 had cancer of a gingivo-buccal sulcus, 18 patients had cancer of the retro-molar area, and 15 had cancer of the bucco-labial area (Table 1).Tumor stage was T1 in 36 patients and T2 in 97 patients (Table 1).

All medical research that involves human participants, tissues and data should undergo ethics review before it commences. This study was approved by the research ethics board committee.

Treatment policies

The activity of the grain was 175 MBq ± 10% per seed, and single plane implantations were used routinely. The target dose area prescribed was deigned to cover the lesion with a 0.5 cm margin in there shape of an oral hexagonal area (PTV). ^{198}Au-grain implantation was performed under local anesthesia, and the entire implantation procedure took about 20 minutes.[14,19] Treatment was by ^{198}Au-grain implantation alone in 75 patients and by ^{198}Au-grain implantation following external irradiation in 58 patients. External irradiation was used to treat patients whose tumor was more than 1 cm thick, and it was performed via a single lateral port (4 MV x-ray) to irradiate the tumors and the upper cervical region. The patients treated by ^{198}Au-grain implantation alone received a total radiation decay dose of 68–99 Gy (mean: 70 Gy in 7 days). The radiation dose was changed following the shape of PTV and the patients who were treated by a combination of BT and EBRT received an average BT dose of 60 Gy in 7 days after EBRT with 10–48 Gy (mean: 28 Gy) over 1–5 weeks. The ^{198}Au grains were arranged in a single plane. Gross tumor area ranged from 2.4 cm^2 to 9 cm^2 (mean: 5.0 cm^2), and the clinical target areas ranged from 6 cm^2 to 15 cm^2.

Table 1. Sub-sites and stages of buccal mucosa carcinoma

	Stage I	Stage II	Total
Mucosa of the Lips	2	13	15
Cheek Mucosa	23	54	77
Retromolar Area	4	14	18
Bucco-Alveolar Sulci	7	16	23
Total	36	97	133

Assessment of the results of treatment

Cause-specific survival was calculated by the Kaplan-Meier method, and differences were analyzed for significance by the log-rank (Mantel-Cox) test. Post-treatment QOL and toxicity was assessed at outpatient clinically based on the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC).[12,20]

At outpatient clinic, oral symptoms such as pain, swallowing problem sensory and speech disturbances dry mouth were inquired. All the clinical findings and complains of the patients were checked at the clinical chart.

RESULTS

The cause-specific 5-year survival rate of the stage I patients and stage II patients was 80% and 81%, respectively, and the difference was not significant ($p = 0.084$) (Fig. 1). The cause-specific 5-year survival rate according to sub-site of the buccal mucosa was 100%, 81%, 79%, and 76% for the mucosa of upper and lower lips, retromolar areas, cheek mucosa and bucco-alveolar sulcus, respectively. There was a significant difference between survival rate of the patients with cancer of the mucosa of the lips and of the other three sub-sites (Fig. 2). There was no difference in the primary control between ^{198}Au-grain implantation alone group and ^{198}Au-grain implantation+EBRT group.

There was a recurrence after primary treatment in 33 patients between 3 months and 8 years (mean: 18 months) after ^{198}Au-grain implantation. Salvage surgery was attempted in 15 patients of a primary recurrence and was successful in 11 of them. Salvage ^{198}Au-grain BT was performed in 7 patients and was successful in 4 of them, and salvage was achieved in another patient by surgery after recurrence following second ^{198}Au-grain BT. Ten patients refused further treatment for their recurrence, and all of them died of their disease. As a result, the final failure at the site of the primary lesion occurred in 17 of the 133 patients. Early mucositis developed in every case in which there was no recurrence at the site of the primary lesion, but it resolved within 2 to 4 months (median: 2.5 months) following BT. Follow-up of the mucosal condition and oral condition of 67 patients was possible for more than 5 years after BT.

The mean and median follow-up periods after BT were 5

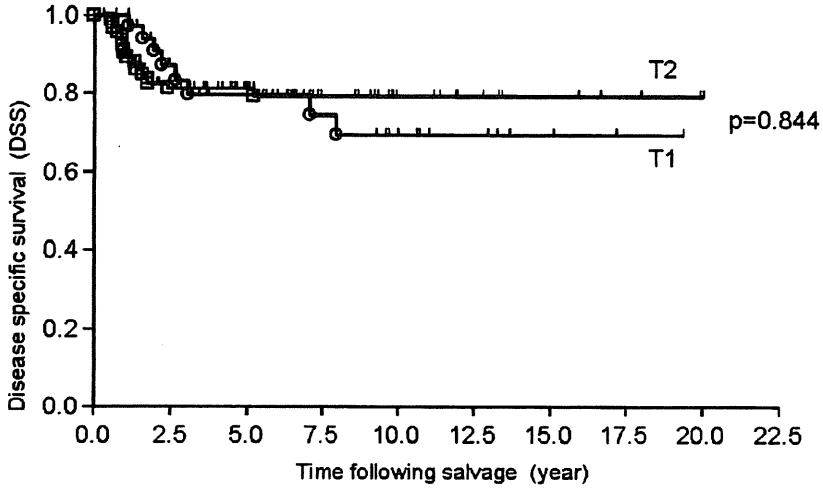

Fig. 1. Cause-specific survival of patients with stage I (T1) and stage II (T2) bucca mucosa cancer.

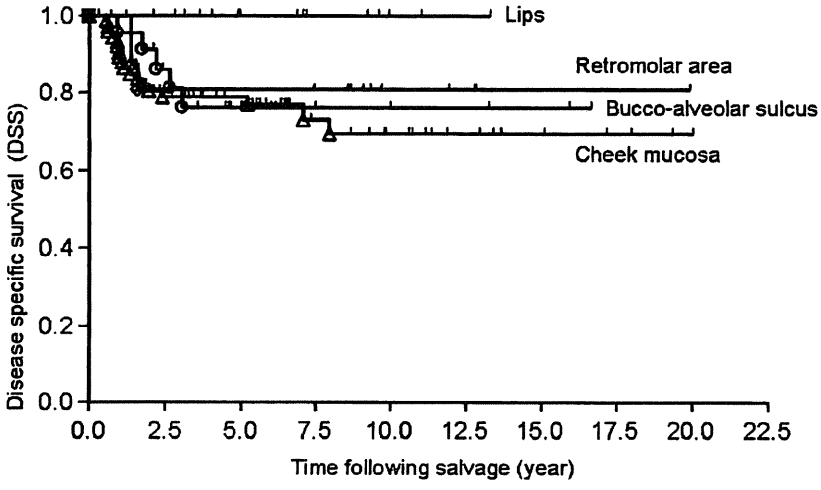

Fig. 2. Cause-specific survival according to 4 sub-sites of the buccal mucosa.

years 11 months and 5 years 1 months (range: 3 months to 20 years). Sixty-five cases were followed up long enough for over 5 years after BT and without recurrence and it was possible to evaluate these patients for late radiation-induced morbidities. There was no difference in the toxicity between BT alone group and BT+EBRT group. Transient post-treatment mucosal ulceration occurred 3 months to 7 years (mean: 12 months) after BT in 15 patients, but it resolved within one to 25 months (median: 4 months) in response to conservative treatment. EBRT had been used to treat 11 of these 15 patients prior to BT, and the average EBRT dose was 28 Gy.

Osteoradionecrosis occurred 4 to 10 years (mean: 6 years) after BT in 8 patients, and surgical mandibular sequesterotomy was necessary in one of them. No patients required surgical mandibulectomy. Six of the 8 patients had received an average EBRT dose of 37 Gy prior to BT. Ten patients complained of mild dry mouth, and all of them were cases treated by BT after unilateral EBRT. Twenty-six patients were followed up for more than 10 years, and none of them developed complications. None of these 26 patients complained of any symptom of H&N35. In addition no patients complained of any symptom of QLQ-C-30 after 10 years. There were no bone complications or any decrease in the primary control rate after we reduced the EBRT dose to below 30 Gy in 1992. Mucous membrane complications became minimal after reducing the external dose to below 30 Gy, but Grade 1 mucous membrane morbidity developed in 2 of the 18 cases. Ten of the 26 patients followed up for over 10 years were found to have late grade 1 soft tissue complications at their last follow-up.

Cervical lymph node metastasis occurred 2 to 68 months (mean: 10 months) after BT in 34 patients, and radical neck dissection was successful in 22 (76%) of the 29 cases in

which it was performed. Three cases of neck node metastasis were treated by EBRT up to 60 Gy, but treatment was unsuccessful, and the patients died of their disease. Two patients who refused treatment for neck metastasis also died of their disease.

Fifty-seven second primary cancers were diagnosed in 44 patients following BT for the primary buccal mucosa cancer, and they included 27 head and neck cancers, 6 gastric cancers, and 5 cancers each of the esophagus and the lung. Radiation-induced cancer was diagnosed in two patients 11 years and 13 years, respectively, after treatment for buccal mucosa carcinoma (fibrosarcoma and squamous cell carcinoma in both cases). One of two cases of radiation-induced cancer was successfully treated by surgery.

DISCUSSION

Treatment with ionizing radiation is expected to have a lethal effect on tumor cells but spare normal tissue. However, we are now seeing moderate to severe late complications in patients cured by RT, and their incidence and severity increase with time.[12] Moreover, the late effects in normal tissues often cannot be predicted on the basis of the acute reactions.[12]

BT delivers a high radiation dose to only a limited volume and spares the surrounding normal tissues. It is a very effective local treatment for early oral cancer and yields results comparable to those obtained by surgery.[14–16] LDR-BT has long been demonstrated to be superior to surgery as a treatment for oral cavity cancer in terms of both preservation of structure and function and a low incidence of complications.[14–19,21,22] LDR-BT is also a useful curative treatment modality for patients with severe comorbidity in whom surgery is contraindicated.[22,23] Disease control of oral cancers and the incidence of complications after LDR-BT have been reported to be unrelated to the severity of comorbid diseases.[23] There have been few reports of studies that have focused on the long-term results in terms of QOL and late complications following BT for oral cancers.[7] Pernot *et al.* reported greater than grade-2 soft tissue complication rate of 4.1% and a greater than grade-2 bone complication rate of 6.7% after ^{192}Ir LDR-BT for cancer of the oral cavity and oropharynx.[15] Our analysis of the results of ^{198}Au-grain BT showed rather high rates of greater than grade-2 soft tissue and bone complications of 11% and 6%, respectively. However, since the target volume was rather small, the area and duration of the complications were small and transient, with most resolving in response to conservative treatment. Ten patients had grade 1 soft tissue complications more than 10 years post-treatment had no complaints at the time of their final follow-up examination.

Based on the results of our study, the volume of the organ and/or tissue irradiated was concluded to be an important as fractionation in determining whether ^{198}Au-grain BT induced late adverse effects.[24] BT with ^{198}Au-grains allowed us to plan a smaller treatment target area than EBRT and to irradiate only a limited area of normal tissue. Moreover, all post-treatment soft tissue and bone complications developed within 10 years following treatment, and there were no new complications or aggravation of complications thereafter. Even though the incidence of soft tissue and bone complications was not low, the area of the complications was minimal, and they resolved within a few months in response to conservative treatment. The volume involved in the cases treated by ^{198}Au-grain BT was thought to be as limited as in minimal surgery. Moreover, after the implementation of the policy of treating with 4 MV x-ray doses below 26 Gy in 2.6 weeks, the late soft tissue and mandibular complications have become minimal and acceptable.

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