Table 47 Endoscopic surgery

Endoscopic surgery	Cases (%)
None	1899 (84.4%)
Thoracoscopy-assisted	187 (8.3%)
Laparoscopy-assisted	73 (3.2%)
Thoracoscopy + Laparoscopy-assisted	64 (2.8%)
Mediastinoscopy-assisted	20 (0.9%)
Thoracoscopy + Mediastinoscopy-assisted	0
Laparoscopy + Mediastinoscopy-assisted	1 (0.0%)
Others	3 (0.1%)
Unknown	4 (0.2%)
Total	2251
Missing	259

Table 48 Fields of lymph node dissection according to the location of the tumor

*** Excluding pharynx and missing 38 cases of locations**

Locations	Cevical		Upper thoracic		Middle thoracic		Lower thoracic		Abdominal		EGJ		Total	
Region of lymphadenectomy	Cases (%)		Cases (%)		Cases (%)		Cases (%)		Cases (%)		Cases (%)		Cases (%)	
None	7	(10.3%)	7	(3.0%)	45	(4.3%)	17	(2.4%)	5	(3.6%)	0		81	(3.8%)
C	21	(30.9%)	2	(0.8%)	3	(0.3%)	1	(0.1%)	0		0		27	(1.3%)
C+UM	14	(20.6%)	2	(0.8%)	3	(0.3%)	0		0		0		19	(0.9%)
C+UM+MLM	2	(2.9%)	7	(3.0%)	13	(1.3%)	9	(1.3%)	0		0		31	(1.4%)
C+UM+MLM+A	15	(22.1%)	132	(55.9%)	467	(45.0%)	219	(30.9%)	8	(5.7%)	2	(5.9%)	843	(39.3%)
C+UM+A	3	(4.4%)	1	(0.4%)	1	(0.1%)	2	(0.3%)	0		0		7	(0.3%)
C+MLM	0		0		0		0		0		0		0	
C+MLM+A	0		1	(0.4%)	3	(0.3%)	1	(0.1%)	0		0		5	(0.2%)
C+A	0		1	(0.4%)	2	(0.2%)	2	(0.3%)	1	(0.7%)	0		6	(0.3%)
UM	0		3	(1.3%)	1	(0.1%)	3	(0.4%)	0		0		7	(0.3%)
UM+MLM	0		6	(2.5%)	19	(1.8%)	8	(1.1%)	1	(0.7%)	0		34	(1.6%)
UM+MLM+A	3	(4.4%)	57	(24.2%)	404	(38.9%)	334	(47.1%)	28	(20.0%)	3	(8.8%)	829	(38.7%)
UM+A	0		1	(0.4%)	4	(0.4%)	3	(0.4%)	0		0		8	(0.4%)
MLM	0		2	(0.8%)	4	(0.4%)	6	(0.8%)	4	(2.9%)	2	(5.9%)	18	(0.8%)
MLM+A	1	(1.5%)	8	(3.4%)	43	(4.1%)	83	(11.7%)	56	(40.0%)	18	(52.9%)	209	(9.7%)
A	0		0		14	(1.3%)	18	(2.5%)	35	(25.0%)	9	(26.5%)	76	(3.5%)
Unknown	2	(2.9%)	6	(2.5%)	12	(1.2%)	3	(0.4%)	2	(1.4%)	0		25	(1.2%)
Total	68		236		1038		709		140		34		2144	
Missing	6		32		108		83		15		3		247	

C: bilateral cervical nodes

UM: upper mediastinal nodes

MLM: middle-lower mediastinal nodes

A: abdominal nodes

Table 49 Extent of lymph node dissection

Grade of dissection (D)	Cases (%)	
DX	47	(2.1%)
D0	121	(5.4%)
DI	292	(13.1%)
DII	1023	(45.8%)
DIII	751	(33.6%)
Total	2234	
Missing	276	

Table 50 Reconstruction route

Reconstruction route	Cases (%)	
None	30	(1.4%)
Antethoracic	212	(9.6%)
Retrosternal	736	(33.3%)
Intrathoracic	348	(15.7%)
Posterior mediastinal	826	(37.3%)
Others	38	(1.7%)
Unknown	23	(1.0%)
Total	2213	
Missing	278	

Table 51 Organs used for reconstruction

Organs used for reconstruction	Cases (%)	
None	36	(1.5%)
Whole stomach	227	(9.7%)
Gastric tube	1758	(74.9%)
Jejunum	107	(4.6%)
Free jejunum	34	(1.4%)
Colon	101	(4.3%)
Free colon	9	(0.4%)
Skin graft	1	(0.0%)
Others	67	(2.9%)
Unknown	8	(0.3%)
Total lesions	2348	
Total cases	2248	
Missing	262	

Table 58 Histological classification

Histological classification	Cases (%)	
Not examined	6	(0.3%)
SCC	1985	(88.9%)
SCC	226	(10.1%)
Well diff.	450	(20.2%)
Moderately diff.	944	(42.3%)
Poorly diff.	365	(16.3%)
Adenocarcinoma	73	(3.3%)
Barrett's adenocarcinoma	37	(1.7%)
Adenosquamous cell carcinoma	10	(0.4%)
(Co-existing)	1	(0.0%)
(Mucoepidermoid carcinoma)	1	(0.0%)
Adenoid cystic carcinoma	2	(0.1%)
Basaloid carcinoma	24	(1.1%)
Undiff. carcinoma (small cell)	9	(0.4%)
Undiff. carcinoma	6	(0.3%)
Other carcinoma	1	(0.0%)
Sarcoma	17	(0.8%)
Carcinosarcoma	4	(0.2%)
Malignant melanoma	6	(0.3%)
Dysplasia	5	(0.2%)
Other	22	(1.0%)
Unkown	24	(1.1%)
Total	2233	
Missing	277	

SCC: Squamous cell carcinoma

Table 59 Depth of tumor invasion

pT-category	Cases (%)	
pTX	7	(0.3%)
pT0	35	(1.6%)
pTis	33	(1.5%)
pT1a	175	(7.8%)
pT1b	517	(23.2%)
pT2	314	(14.1%)
pT3	959	(42.9%)
pT4	154	(6.9%)
Other	0	
Unknown	39	(1.7%)
Total	2233	
Missing	277	

Table 60 Subclassification of superficial carcinoma

Subclassification	Cases (%)	
Not superficial carcinoma	1487	(66.9%)
m1 (ep)	35	(1.6%)
m2 (lpm)	64	(2.9%)
m3 (mm)	101	(4.5%)
sm1	70	(3.1%)
sm2	113	(5.1%)
sm3	232	(10.4%)
Unknown	122	(5.5%)
Total	2224	
Missing	286	

ep: epithelium

lpm: lamina propria muosa mm: muscularis mucosa

Table 61 Pathological grading of lymph node metastasis

Lymph node metastasis	Cases (%)	
n (-)	910	(41.7%)
n1 (+)	329	(15.1%)
n2 (+)	539	(24.7%)
n3 (+)	181	(8.3%)
n4 (+)	177	(8.1%)
Unknown	44	(2.0%)
Total	2180	
Missing	330	

Table 62 Numbers of the metastatic nodes

Numbers of lymph node metastasis	Cases (%)	
0	1176	(46.9%)
1-3	737	(29.4%)
4-7	288	(11.5%)
8-	223	(8.9%)
Unknown	85	(3.4%)
Total	2509	
Missing	1	

Table 63 Pathological findings of distant organ metastasis

Distant metastasias (M)	Cases (%)	
MX	29	(1.3%)
M0	2171	(96.6%)
M1	48	(2.1%)
Total	2248	
Missing	262	

Table 64 Residual tumor

Residual tumor (R)	Cases (%)	
RX	117	(5.3%)
R0	1797	(82.0%)
R1	141	(6.4%)
R2	124	(5.7%)
Unknown	12	(0.5%)
Total	2191	
Missing	319	

Table 75 Causes of death

Cause of death	Cases (%)	
Death due to recurrence	780	(70.0%)
Death due to other cancer	52	(4.7%)
Death due to other disease (rec+)	41	(3.7%)
Death due to other disease (rec-)	122	(11.0%)
Death due to other disease (rec?)	23	(2.1%)
Death within 30 days after operation	25	(2.2%)
Death 31 days or more after operation	52	(4.7%)
Unknown	19	(1.7%)
Total of death cases	1114	
Missing	14	

rec: recurrence

Operative death means death within 30 days after operation in or out of hospital.

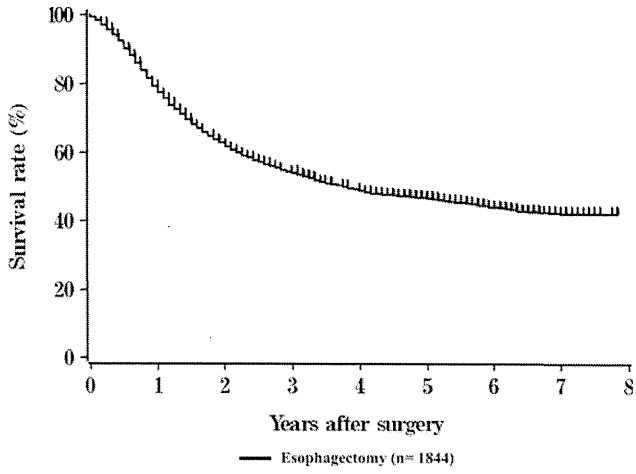
Operative mortality : 1.0%

Follow-up period (years)	
Median (min - max)	2.75 (0.00 - 7.41)

Table 76 Initial recurrent lesion

Initial recurrence lesion of fatal cases	Cases (%)	
Lymph node	509	(41.4%)
Lung	200	(16.3%)
Liver	176	(14.3%)
Bone	106	(8.6%)
Brain	29	(2.4%)
Primary lesion	95	(7.7%)
Dissemination	56	(4.6%)
Anastomotic region	2	(0.2%)
Others	48	(3.9%)
Unknown	8	(0.7%)
Total of recurrence lesion	1229	
Total	1081	
Missing	347	

Fig. 8 Survival of patients treated by esophagectomy



	Years after surgery							
	1	2	3	4	5	6	7	8
Esophagectomy	**78.9%**	**62.8%**	**54.4%**	**48.9%**	**46.6%**	**44.0%**	**42.2%**	**41.9%**

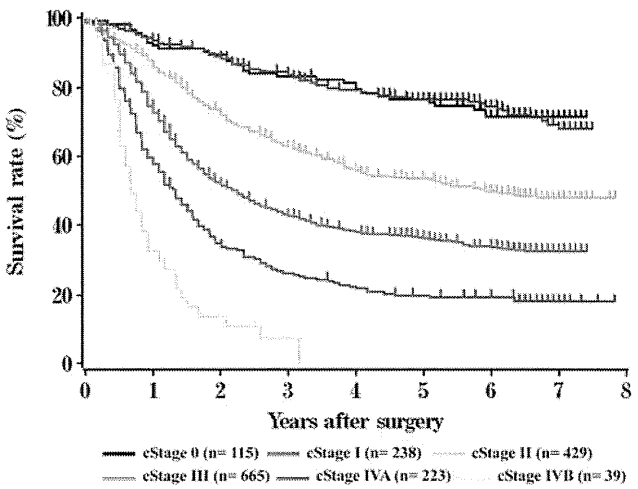


Fig. 9 Survival of patients treated by esophagectomy in relation to clinical stage (JSED-cTNM 9th)

	Years after surgery							
	1	2	3	4	5	6	7	8
cStage 0	92.9%	89.4%	83.0%	79.3%	76.5%	71.2%	71.2%	71.2%
cStage I	94.2%	89.0%	84.4%	79.3%	76.3%	74.3%	69.1%	67.7%
cStage II	87.5%	73.6%	62.9%	55.8%	53.4%	49.7%	47.9%	47.9%
cStage III	74.3%	52.3%	43.0%	37.9%	36.3%	33.7%	32.4%	32.4%
cStage IVA	59.1%	34.6%	26.2%	21.7%	19.7%	19.2%	17.9%	17.9%
cStage IVB	32.7%	13.6%	7.3%	-	-	-	-	-

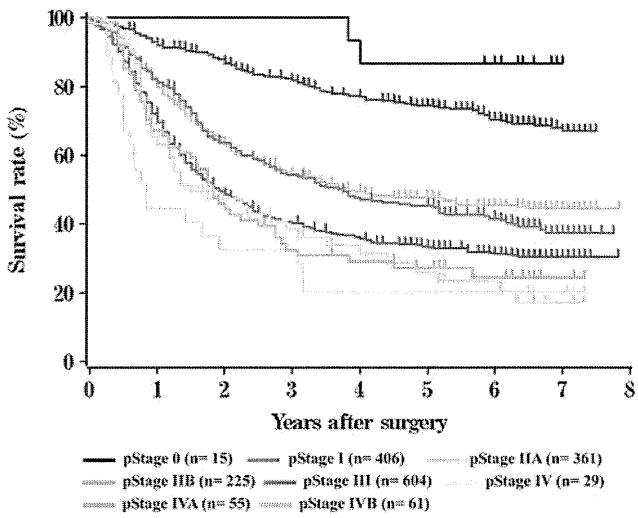


Fig. 10 Survival of patients treated by esophagectomy in relation to clinical stage (UICC-cTNM 5th)

	Years after surgery							
	1	2	3	4	5	6	7	8
cStage 0	93.3%	93.3%	93.3%	86.7%	86.7%	86.7%	86.7%	-
cStage I	92.9%	87.8%	82.2%	76.9%	74.3%	67.8%	66.8%	-
cStage IIA	81.9%	65.1%	55.0%	49.3%	47.5%	45.3%	44.4%	44.4%
cStage IIB	82.0%	63.6%	54.2%	47.0%	45.1%	41.5%	37.4%	37.4%
cStage III	71.6%	49.3%	40.5%	35.6%	33.3%	31.4%	30.4%	30.4%
cStage IV	44.4%	32.3%	28.3%	20.2%	20.2%	20.2%	20.2%	-
cStage IVA	65.0%	47.2%	38.4%	31.1%	25.9%	23.3%	20.2%	20.2%
cStage IVB	67.2%	45.9%	32.5%	29.0%	27.0%	24.3%	24.3%	24.3%

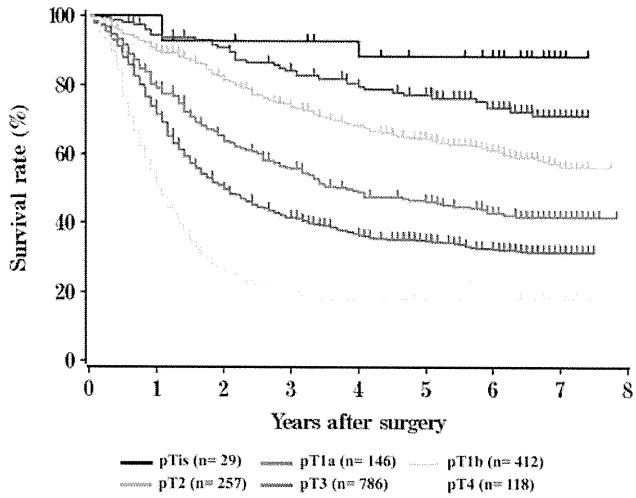


Fig. 11 Survival of patients treated by esophagectomy in relation to the depth of tumor invasion (JSED-pTNM 9th: pT)

	Years after surgery							
	1	2	3	4	5	6	7	8
pTis	100.0%	92.6%	92.6%	88.2%	88.2%	88.2%	88.2%	88.2%
pT1a	94.3%	90.7%	84.1%	79.5%	77.1%	73.4%	71.0%	71.0%
pT1b	90.8%	82.5%	74.5%	68.4%	64.6%	61.2%	57.1%	56.2%
pT2	80.1%	65.2%	56.1%	48.8%	46.2%	42.7%	41.6%	41.6%
pT3	73.3%	50.9%	41.4%	36.3%	34.9%	32.6%	31.5%	31.5%
pT4	53.3%	27.0%	21.2%	18.0%	18.0%	18.0%	18.0%	18.0%

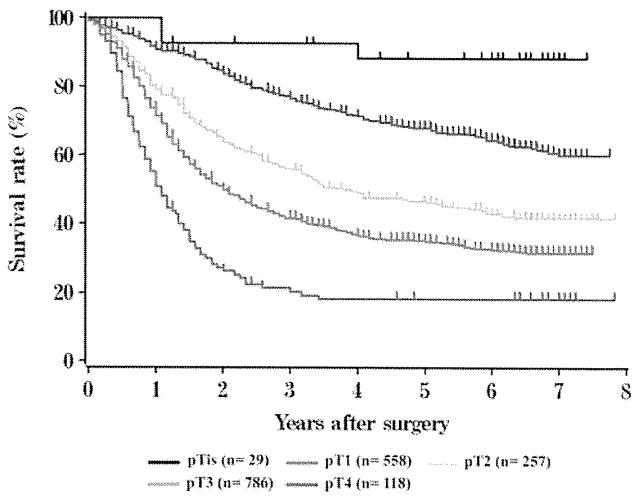


Fig. 12 Survival of patients treated by esophagectomy in relation to the depth of tumor invasion (UICC-pTNM 5th: pT)

	Years after surgery							
	1	2	3	4	5	6	7	8
pTis	100.0%	92.6%	92.6%	88.2%	88.2%	88.2%	88.2%	88.2%
pT1	91.8%	84.6%	77.0%	71.3%	67.8%	64.3%	60.7%	60.0%
pT2	80.1%	65.2%	56.1%	48.8%	46.2%	42.7%	41.6%	41.6%
pT3	73.3%	50.9%	41.4%	36.3%	34.9%	32.6%	31.5%	31.5%
pT4	53.3%	27.0%	21.2%	18.0%	18.0%	18.0%	18.0%	18.0%

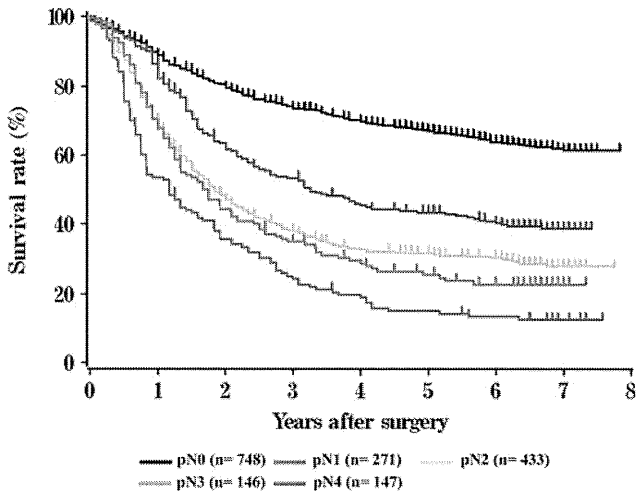


Fig. 13 Survival of patients treated by esophagectomy in relation to lymph node mentastasis (JSED-pTNM 9th: pN)

	Years after surgery							
	1	2	3	4	5	6	7	8
pN0	89.8%	80.5%	74.1%	69.6%	67.0%	63.7%	61.8%	61.2%
pN1	86.3%	63.5%	53.4%	45.3%	43.3%	40.6%	38.5%	38.5%
pN2	69.8%	48.4%	38.2%	32.7%	31.7%	30.4%	28.0%	28.0%
pN3	69.7%	44.2%	34.9%	28.8%	25.5%	22.8%	22.8%	22.8%
pN4	53.5%	35.7%	25.0%	18.9%	15.0%	13.3%	12.4%	12.4%

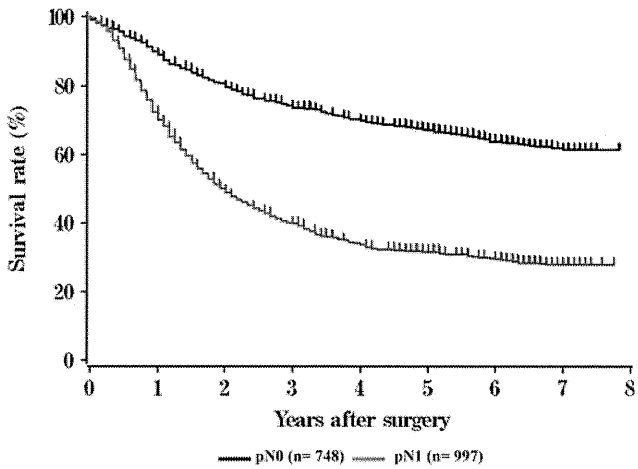


Fig. 14 Survival of patients treated by esophagectomy in relation to lymph node mentastasis (UICC-pTNM 5th: pN)

	Years after surgery							
	1	2	3	4	5	6	7	8
pN0	89.8%	80.5%	74.1%	69.6%	67.0%	63.7%	61.8%	61.2%
pN1	72.0%	50.1%	40.0%	33.6%	31.6%	29.6%	27.8%	27.8%

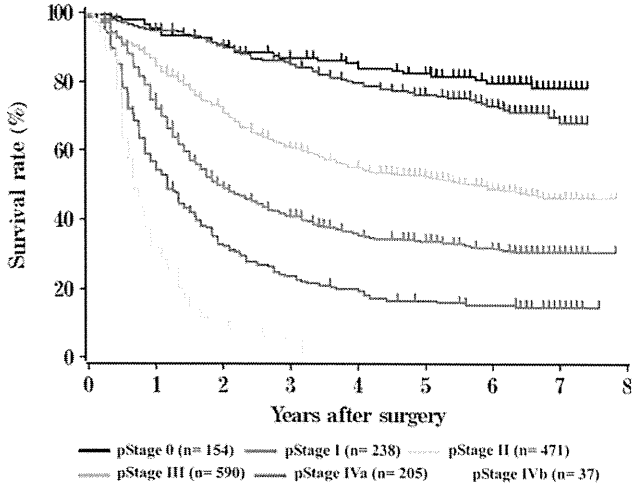


Fig. 15 Survival of patients treated by esophagectomy in relation to pathological stage (JSED-pTNM 9th)

	Years after surgery							
	1	2	3	4	5	6	7	8
pStage 0	95.3%	90.5%	86.9%	83.9%	82.3%	79.6%	78.3%	78.3%
pStage I	94.8%	90.8%	85.8%	79.7%	76.3%	73.0%	69.8%	68.1%
pStage II	86.6%	72.7%	61.1%	54.9%	52.6%	48.9%	46.2%	46.2%
pStage III	74.4%	49.8%	41.0%	35.3%	33.7%	31.7%	30.5%	30.5%
pStage IVa	55.8%	32.7%	23.6%	19.3%	16.5%	15.3%	14.6%	14.6%
pStage IVb	31.7%	11.5%	5.8%	0.0%	-	-	-	-

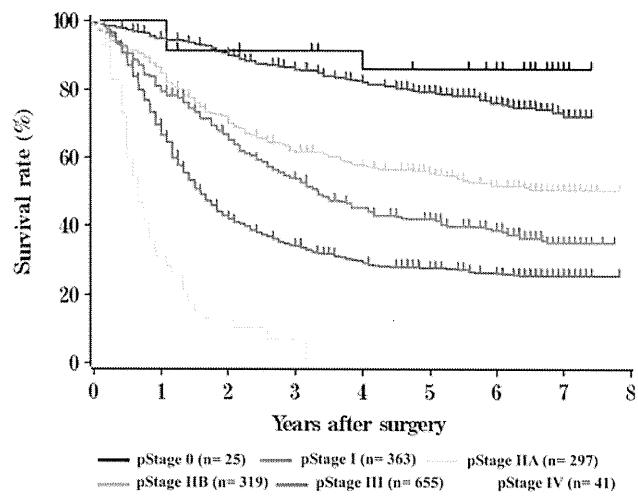


Fig. 16 Survival of patients treated by esophagectomy in relation to pathological stage (UICC-pTNM 5th)

	Years after surgery							
	1	2	3	4	5	6	7	8
pStage 0	100.0%	91.3%	91.3%	85.9%	85.9%	85.9%	85.9%	-
pStage I	94.6%	90.5%	86.4%	82.0%	79.1%	75.8%	73.2%	72.1%
pStage IIA	86.1%	72.1%	62.0%	57.6%	55.8%	51.6%	50.5%	50.5%
pStage IIB	80.8%	66.7%	54.0%	45.3%	41.8%	38.7%	34.9%	34.9%
pStage III	69.0%	42.9%	34.2%	29.1%	27.7%	26.3%	25.4%	25.4%
pStage IV	31.1%	13.0%	6.9%	-	-	-	-	-

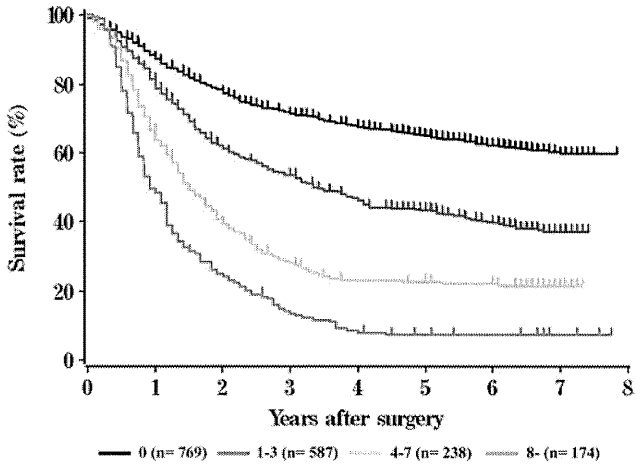


Fig. 17 Survival of patients treated by esophagectomy in relation to number of mentastatic node

	Years after surgery							
	1	2	3	4	5	6	7	8
0	88.3%	78.6%	71.8%	67.5%	64.9%	62.1%	60.2%	59.7%
1-3	81.2%	62.1%	53.4%	46.1%	43.3%	39.8%	37.1%	37.1%
4-7	66.3%	40.7%	28.6%	23.2%	22.7%	22.1%	21.5%	21.5%
8-	48.9%	24.9%	14.1%	8.0%	7.3%	7.3%	7.3%	7.3%

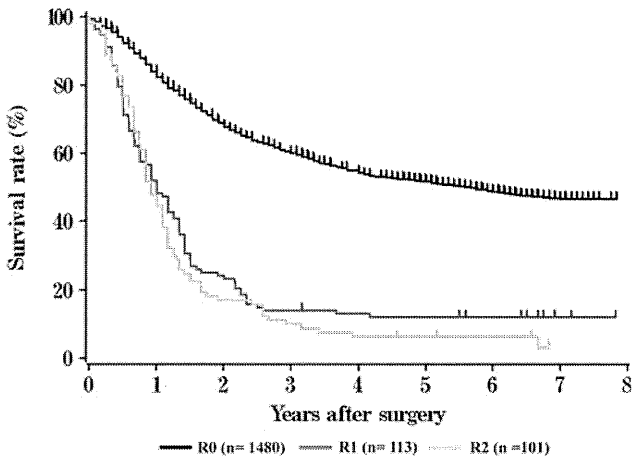


Fig. 18 Survival of patients treated by esophagectomy in relation to residual tumor (R)

	Years after surgery							
	1	2	3	4	5	6	7	8
R0	83.6%	68.8%	60.4%	54.2%	51.6%	48.8%	46.9%	46.6%
R1	52.0%	24.1%	13.9%	12.9%	11.9%	11.9%	11.9%	11.9%
R2	45.5%	16.9%	9.8%	6.1%	6.1%	6.1%	3.1%	-

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Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. e49–e56, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2011.01.022

CLINICAL INVESTIGATION **Gynecologic Cancer**

PROSPECTIVE MULTI-INSTITUTIONAL STUDY OF DEFINITIVE RADIOTHERAPY WITH HIGH-DOSE-RATE INTRACAVITARY BRACHYTHERAPY IN PATIENTS WITH NONBULKY (<4-CM) STAGE I AND II UTERINE CERVICAL CANCER (JAROG0401/JROSG04-2)

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Purpose: To determine the efficacy of a definitive radiotherapy protocol using high-dose-rate intracavitary brachytherapy (HDR-ICBT) with a low cumulative dose schedule in nonbulky early-stage cervical cancer patients, we conducted a prospective multi-institutional study.

Methods and Materials: Eligible patients had squamous cell carcinoma of the intact uterine cervix, Federation of Gynecologic Oncology and Obstetrics (FIGO) stages Ib1, IIa, and IIb, tumor size <40 mm in diameter (assessed by T2-weighted magnetic resonance imaging), and no pelvic/para-aortic lymphadenopathy. The treatment protocol consisted of whole-pelvis external beam radiotherapy (EBRT) of 20 Gy/10 fractions, pelvic EBRT with midline block of 30 Gy/15 fractions, and HDR-ICBT of 24 Gy/4 fractions (at point A). The cumulative biologically effective dose (BED) was 62 Gy_{10} ($\alpha/\beta = 10$) at point A. The primary endpoint was the 2-year pelvic disease progression-free (PDPF) rate. All patients received a radiotherapy quality assurance review.

Results: Between September 2004 and July 2007, 60 eligible patients were enrolled. Thirty-six patients were assessed with FIGO stage Ib1; 12 patients with stage IIa; and 12 patients with stage IIb. Median tumor diameter was 28 mm (range, 6–39 mm). Median overall treatment time was 43 days. Median follow-up was 49 months (range, 7–72 months). Seven patients developed recurrences: 3 patients had pelvic recurrences (2 central, 1 nodal), and 4 patients had distant metastases. The 2-year PDPF was 96% (95% confidence interval [CI], 92%–100%). The

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Presented at the 12th Annual Meeting of the Japanese Group of Brachytherapy/Japanese Society for Therapeutic Radiology and Oncology (JGB/JASTRO), Tokyo, Japan, May 15-16, 2010; and at the 52nd Annual Meeting of the American Society for Radiation Oncology, San Diego, CA, Oct 31–November 4, 2010.

This study was supported by grants from Ministry of Health, Labor and Welfare (Grant-in-Aid for Cancer Research nos. 16-12 and 20-5), Ministry of Health, and the Japan Society for the Promotion of Sciences (No. 16591214, 18591387, and 21591614).

Conflict of interest: none.

Acknowledgments—The authors thank Ms. Asazawa for constant assistance.

Received June 20, 2010, and in revised form Nov 22, 2010. Accepted for publication Jan 10, 2011.

2-year disease-free and overall survival rates were 90% (95% CI, 82%–98%) and 95% (95% CI, 89%–100%), respectively. The 2-year late complication rates (according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer of Grade ≥1) were 18% (95% CI, 8%–28%) for large intestine/rectum, 4% (95% CI, 0%–8%) for small intestine, and 0% for bladder. No Grade ≥3 cases were observed for genitourinary/gastrointestinal late complications.

Conclusions: These results suggest that definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED, 62 Gy_{10} at point A) can provide excellent local control without severe toxicity in nonbulky (<4-cm) early-stage cervical cancer. © **2012 Elsevier Inc.**

Carcinoma of the cervix, Radiotherapy, High-dose-rate, Intracavitary brachytherapy, Dose response.

INTRODUCTION

Numerous retrospective studies of definitive radiotherapy (RT) have reported favorable local control with an acceptable level of toxicity for patients with early-stage cervical cancer (1–4). A randomized clinical trial (RCT) performed in Italy in the 1990s revealed no significant difference in overall survival between patients treated with surgery and those treated with definitive RT (5). As a result, definitive radiotherapy has been accepted as one of the treatment options for early-stage cervical cancer (6).

Standard definitive RT for uterine cervical cancer consists of external beam RT (EBRT) to the whole pelvis and intracavitary brachytherapy (ICBT) (6). Several RCTs have demonstrated that high-dose-rate ICBT (HDR-ICBT) achieves rates of local control and late toxicity that are similar to those of low-dose-rate ICBT (LDR-ICBT) (7,8). Therefore, HDR-ICBT will likely replace LDR-ICBT as the standard of treatment, with several advantages over the LDR-ICBT. Dosing schedules of HDR-ICBT (*i.e.*, total dose and fractions in combination with EBRT) differ substantially among various countries, both in clinical practice (3, 4, 7–20) and in published guidelines (21, 22). Table 1 lists various schedules for definitive RT with HDR-ICBT along with pelvic control rates for stage I and II cervical cancer (3, 4, 7–22). Immediately evident is the lack of a clear dose-response relationship between biologically effective dose (BED) at point A and pelvic control, which has been previously noted (23).

We have identified two possible factors that explain the lack of a clear dose-response relationship in these retrospective studies. The first is potential bias in the doses delivered to each patient; that is, patients with a poor response to RT might have received higher total doses than good responders. Second, most of these studies did not include tumor size assessment, which was another serious limitation for comparison among the various series. Tumor size is one of the most important parameters affecting local control in radiotherapy for cervical cancer and may vary widely even within the same Federation of Gynecologic Oncology and Obstetrics (FIGO) stage (24). Therefore, a prospective study based on appropriate tumor size assessment and a fixed dose schedule would seem warranted to determine an optimum dosing schedule of HDR-ICBT.

Magnetic resonance imaging (MRI) is one of the most useful imaging modalities to evaluate tumor size objectively in cervical cancer (25–27). Toita *et al.* (28) retrospectively analyzed the relationship between local control and tumor diameter as assessed by MRI in a small series. In that series, in patients with American Brachytherapy Society (ABS)-defined early disease (stage I/II, <4 cm) (22), the 3-year actuarial pelvic control rate was 96%, within the dose range of 48 Gy_{10} to 77 Gy_{10} (28). Pelvic control rates by BED values were 5 out of 5 (5/5) for 48 Gy_{10}, 7/7 for 62 Gy_{10} (α/β = 10), 2/2 for 68 Gy_{10}, and 8/9 for 77 Gy_{10} (28). As shown in Table 1, Japanese investigators have reported favorable pelvic control rates with a total BED of 46 to 68 Gy_{10} despite no objective tumor size assessment. These findings suggest that a cumulative dose of 46 to 68 Gy_{10} may be adequate to achieve local control of nonbulky (<4-cm) early-stage cervical cancer.

Based on the above background data, the Japanese Radiation Oncology Study Group (JROSG; http://www.jrosg.jp) conducted a prospective multi-institutional study to assess the efficacy and toxicity of a definitive RT schedule with low cumulative doses in patients with nonbulky stage I and II uterine cervical cancer. We report herein the endpoint results of that prospective study.

METHODS AND MATERIALS

Patient eligibility criteria

Eligible patients had histologically proven squamous cell carcinoma of the intact uterine cervix and FIGO stage Ib1, IIa, or IIb disease. Study patients were between 20 and 85 years of age. A complete physical examination, a pelvic examination performed without anesthesia, and a chest X-ray were required to determine the clinical stage. Patients also were required to have cervical tumors less than 40 mm in diameter, assessed by T_2-weighted MRI, and negative pelvic and para-aortic lymph nodes (less than 10 mm in shortest diameter), as determined by computed tomography (CT). The CT and MRI studies had to be preformed within 4 weeks of entry. Patients were also required to have a Zubrod performance score (PS) of 0 to 2 and adequate bone marrow function: white blood cell count ≥3,000/mm^3, absolute neutrophil count ≥1,000/mm^3, and hemoglobin level ≥8.0 g/L (data after transfusion would be acceptable). All patients provided written informed consent.

Protocol treatment

The treatment is shown in Fig. 1, consisting of a combination of EBRT and HDR-ICBT. Interstitial brachytherapy was not allowed. Chemotherapy was also not permitted. EBRT was delivered to a total dose of 50 Gy in 25 fractions over 5 to 6 weeks. The initial 20 Gy was delivered to the whole pelvis. After that, 30 Gy was administered through the same whole-pelvis field with a midline block (MB) 3 to 4 cm in width. The MB was formed with multileaf collimators (MLC) or a custom cerrobend block. The first HDR-ICBT was performed within 10 days after the initial 20 Gy of EBRT. If HDR-ICBT could not be performed in this time interval, the protocol was

Table 1. Schedules and doses of definitive radiotherapy using HDR-ICBT for stage I and/or II cervical cancer

Study (country) (ref)	EBRT (Gy)	HDR-ICBT dose (Gy/fr) or dose range at point A	Total BED (Gy_{10}) or BED range at point A	% or % range of pelvic control (follow-up)	Median follow-up	Comments
Reports						
Nakano *et al.* (Japan) (4)	0–20	29/5–23/4	46–62	86[§]	22 years	Stage IB and II (small)
Teshima *et al.* (Japan) (7)	20	28/4–30/4	63–66	87[§]	11 years	Stage I and II (all)
Hareyama *et al.* (Japan) (8)	0–30	29/5–23/4	46–68	89 (5 years)[‡]	47 months	Stage II (all)
Wang *et al.* (Taiwan) (9)	39.6–45	24/5	82–88	87–94 (5 years)[‡]	5 years	Stage I and II (all)
Wong *et al.* (China) (10)	40	21/3–24/4	84–86	79–89 (5 years)[‡]	4.7 years	Stage I and II (all)
Ozsaran *et al.* (Turkey) (11)	50.4	18/3	88	73 (5 years)[‡]	42 months	CCRT data; stage I and II (all) = 82%
Lee *et al.* (Korea) (3)	40	39/13	95 (median)	95[§]	60 months	Stage IB
Souhami *et al.* (Canada) (12)	45	24/3	96	80–88[§]	50 months	Including CCRT data
Petereit *et al.* (US) (13)	40–50*	45.5–49.5/5[†]	96 (median)[†]	88 (3 years)[‡]	22 months	Stage I and II (≤5 cm)
Sood *et al.* (US) (14)	45	18/2	87	77 (3 years)[§]	3 years	Stage I and II (all): 87%
Anker *et al.* (US) (15)	45	30/5	101	97 (3 years)[‡]	25 months	Including CCRT data; stage I and II (all) = 80%
Patterns of care						
Toita *et al.* (Japan) (16)	30	22–23/4	70–72	–	–	Stage I and II (all)
Jones *et al.* (UK) (17)	40–60	7.5/1–42/6	61–96	–	–	Small volume
Pearce *et al.* (Canada) (18)	45	30/5	101	–	–	Same in all stages
Erickson *et al.* (US) (19)	NS	NS	103 (median)	–	–	All stages combined
Dyk *et al.* (Australia, New Zealand) (20)	45–60	18/3–30/5	73–94	–	–	All stages combined
Recommendations						
Okawa (Japan) (21)	0, 20	29/5, 23/4	46, 60	–	–	Stage I and II (small)
Nag *et al.* (US [ABS]) (22)	20, 45	48/8, 30/5	101	–	–	Stage I and II (nonbulky, <4cm)

Abbreviations: EBRT = external beam radiotherapy; HDR-ICBT = high dose-rate intracavitary brachytherapy; BED = biologically effective dose CCRT = concurrent chemoradiotherapy; fr = fraction; NS = not stated; ABS = American Brachytherapy Society.

* 1.7 Gy/fr.

† Point M.

‡ Actuarial rate.

§ Crude rate.

terminated, and any subsequent treatments (*e.g.*, additional whole-pelvis EBRT without the MB) were at the discretion of the treating physician. Treatment was to be completed within 56 days.

All patients were treated with a photon beam of 6 MV or greater. Both anteroposterior (AP)-posteroanterior (PA) and a four-field techniques were allowed. When the four-field technique was utilized, the portal arrangement was changed to the AP/PA technique after the MB was inserted. A tissue heterogeneity correction was not used in the dose calculation. The upper border of the pelvic field was L4-L5, and the lower border was a transverse line below the obturator foramen. The lateral borders of the AP/PA fields were 1 to 2 cm beyond the lateral margins of the bony pelvis. For the lateral fields, the anterior border was placed at a horizontal line drawn 1 cm anterior to the symphysis pubis anteriorly and a vertical line at the posterior border of the sacrum posteriorly. The upper and lower borders were the same as those for the AP/PA fields. The fields were shaped to shield normal tissues, using a custom block or MLC. Prophylactic para-aortic radiotherapy was not allowed.

HDR-ICBT was performed once per week, administering 24 Gy to point A in four fractions with Ir-192 afterloading machines.

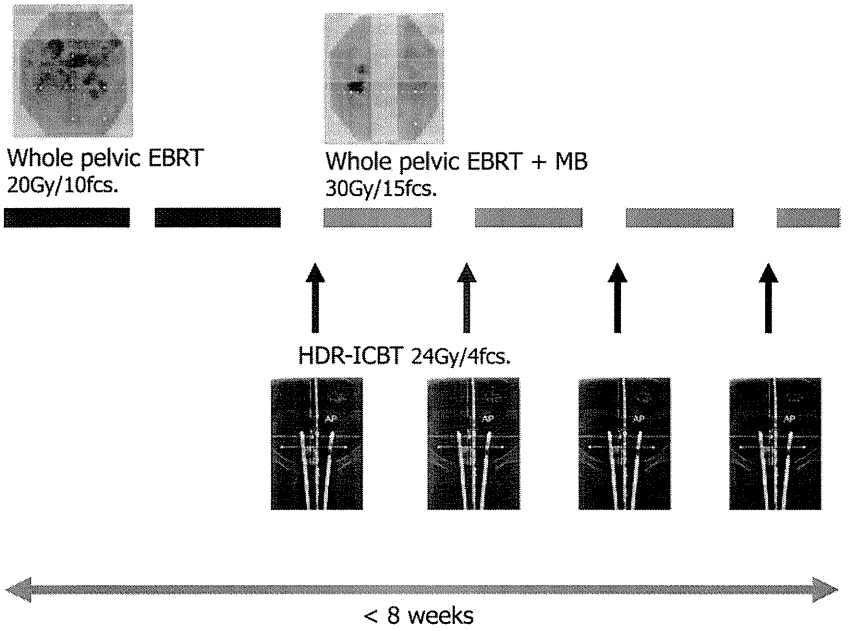

Fig. 1. Treatment schema.

HDR-ICBT delivery was not allowed on the same day as the EBRT. A combination of tandem and ovoid applicators was recommended except as restricted by the vaginal anatomy (*e.g.*, narrow vagina) or significant vaginal disease invasion. Source dwell patterns (*i.e.*, times and positions) were determined according to the Manchester system(29). For determining point A, two alternative rules were established on the basis of the topographical relationships between the tandem and ovoid applicators (30). First, for two A points (left and right), the point associated with the lower dose was to be designated as the prescribed point A. The second rule pertained to the point of origin for the determination of point A. Basically, a coordinate at the external os (usually equivalent to the position of the tandem flange) would be selected as the geographic origin of the point A. In the event the external os was located caudally to the cranial ovoid surface (*e.g.*, roomy vaginal vault), a coordinate of the vaginal vault surface was to be designated as the origin of the vertical level to point A. The concept behind the latter definition is essentially the same as that for point H, proposed by the ABS (22). Dosimetry was performed before each application,using two orthogonal radiographs. The isodoses were plotted, and the doses to the rectum and bladder were calculated according to International Commission on Radiation Units and Measurements (ICRU) 38 criteria (31). Three-dimensional planning with CT and/or MRI was not utilized.

RT was postponed until adverse effects resolved, if one or more of the following adverse events was observed: Grade 4 hematologic toxicity; Grade ≥3 diarrhea, cystitis, nausea, and/or dermatitis; and PS ≥3. If the grade of the toxicities did not decrease after 3 weeks, the planned treatment was terminated.

Quality assurance (QA) reviews of the RT were performed by the QA committee for all patients entered. Treatment charts and radiological data and figures were submitted and reviewed. The results have been published elsewhere (30). Tumor diameter was also reevaluated for all patients at the time of the QA meetings.

Evaluation

Acute side effects were scored according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. Late toxicity was scored by Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity criteria. Patients visited every 3 months during the first 2 years and then every 6 months or annually. Follow-up was to include assessment of late toxicity, pelvic examination, CT of the abdomen and pelvis (every 6 months), MRI of the pelvis (every 6 months), and chest X-ray (every 6 months).

Statistical analysis

The study was approved by the JROSG Protocol Review Committee and the local institutional review boards of the participating institutions.

The primary purpose of this study was to determine if the RT protocol could achieve a local control rate comparable to those previously reported in several retrospective studies. The primary endpoint of this study was the 2-year pelvic disease progression-free (PDPF) rate. Sample size was calculated on the basis of the primary endpoint. We set the expected level for the 2-year PDPF at 85%. To achieve the result within a 95% confidence interval (CI, 75%–95%)for the 2-year PDPF, we calculated that 54 patients would have to be recruited over 3 years, based on the Brookmeyer-Crowly method (32). After the sample size was adjusted by 10% to allow for patient ineligibility or loss, the total sample size was 60 patients.

The secondary endpoints were acute toxicity, treatment completion rate, late complication rate, 2-year disease-specific survival (DSS) rate, 2-year disease-free survival (DFS) rate, 2-year overall survival (OS) rate, and site of recurrence. The PDPF, DSS, DFS, and OS endpoints were measured from the date of treatment start to the date of the events. Estimates of survival distribution and late complication probability were calculated by the Kaplan-Meier method. All analyses were performed using SAS version 8.02 software (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics

Between September 2004 and July 2007, 60 patients were enrolled from 13 institutions. No patient was assessed as

Table 2. Patient characteristics

Characteristics	No. of patients (%)
Age (years)	
Median	73
Range	37–84
<60	11 (18)
60–70	11 (18)
70–80	31 (52)
>80	7 (12)
Performance status	
0	31
1	28
2	1
FIGO stage	
Ib1	36 (60)
IIa	12 (20)
IIb	12 (20)
Tumor size (mm)	
Median	28
Range	6–39
<10	2 (3)
10–19	5 (8)
20–29	23 (39)
30–39	22 (37)
Unable to measure	8 (13)

ineligible. Therefore, 60 patients formed the patient cohort for the analysis. Pretreatment characteristics for the eligible patients are listed in Table 2.

Acute toxicity and compliance

Forty-four patients (72%) were treated on an inpatient basis. The acute toxicity profiles during and after the protocol treatment period (within 90 days) are shown in Table 3. Only one patient experienced toxicity necessitating treatment rest (Grade 3 diarrhea); however, per the patient's treating physician, no protocol treatment postponement was adopted. Eleven patients had treatment rest (median, 4 days; range, 1–7 days). Five patients had treatment rest because of national holidays; 4 patients because of machine trouble; 1 patient because of heart disease; and 1 patient because of preference. Overall treatment time (OTT) ranged from 38 to 55 days, with a median of 43 days. All 60 patients (100%) completed the planned protocol treatment.

Efficacy

Two patients (3%) were lost to follow-up (at 7 and 10 months) within the 24-month follow-up interval. The remaining 58 patients were followed beyond the planned 24 months. The median follow-up time for all 60 patients was 49 months (range, 7–72 months).

Table 3. Acute toxicities

	No. of patients by toxicity grade (n = 60)			
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	17	16	3	0
Neutropenia	15	5	3	0
Anemia	14	2	0	0
Thrombocytopenia	13	0	0	0
Dermatitis	17	4	0	0
Nausea	10	0	0	0
Diarrhea	25	11	1	0
Cystitis	8	5	0	0

Three patients experienced pelvic recurrence: 2 patients had central recurrence, and 1 patient had recurrence in lymph nodes. The estimated 2-year and 3-year PDPF rates were both 96% (95% CI, 92%–100%) (Fig. 2). Five patients developed distant metastases: 4 patients had metastases without pelvic recurrence, and 1 patient had metastases after pelvic recurrence. These cases included recurrence in paraaortic lymph nodes (1 patient), lung (1 patient), liver and subcutaneous tissue (1 patient), and multiple osseous lesions and nodes (2 patients).

Figure 3 shows the incidence of pelvic recurrence and distant recurrence as a function of tumor size subcategories. No pelvic recurrences occurred in patients with tumors less than 30 mm in diameter. The incidence of distant metastasis rose as tumor diameter increased.

Of the 5 patient deaths recorded, 4 patients died from cervical cancer, and 1 patient without cervical cancer recurrence died from an unrelated cause. The estimated 2-year and 3-year DFS rates were both 90% (95% CI, 82%–98%), and the estimated 2-year and 3-year OS rates were both 95% (95% CI, 89%–100%) (Fig. 2).

Dose to organs at risk and late toxicity

In ICBT, median calculated doses to the rectum and bladder according to the ICRU 38 definition were 4.9 Gy (range, 2.2–10.5 Gy) and 4.8 Gy (range, 2.1–12.1 Gy), respectively. Table 4 lists gastrointestinal and genitourinary late toxicity profiles. No patient suffered severe gastrointestinal or genitourinary late toxicities (Grade ≥3). The estimated 2-year and 3-years rates for late toxicities (Grade 1–2) were 16% (95% CI, 6%–26%) and 18% (95% CI, 8%–28%) for the large intestine and rectum, respectively; 0% and 2% (95% CI, 0%–5%), respectively, for the bladder; and 4% (95% CI, 0%–8%) and 7% (95% CI, 4%–14%), respectively, for the small intestine (Fig. 4).

DISCUSSION

To our knowledge, this is the first multi-institutional prospective study to evaluate the efficacy and toxicity of a defined radiotherapy schedule with HDR-ICBT for uterine cervical cancer. Our prospective study demonstrated good 2-year and 3-year PDPF rates of 96% (95% CI, 92%–100%) and an acceptable level of toxicity in 60 patients with nonbulky (<4-cm, assessed by MRI) stage I and II cervical cancer. These results suggest the clinical validity of previously reported results of other Japanese studies (4, 7, 8, 28).

The study by Petereit and Pearcey (23) questioned the published favorable data from Japanese investigators with low cumulative radiotherapy doses, noting that the doses in those Japanese series were less than tumoricidal. The BED of 62 Gy_{10} utilized in our study is equivalent to the 52 Gy used in conventional fractionated radiotherapy (33).

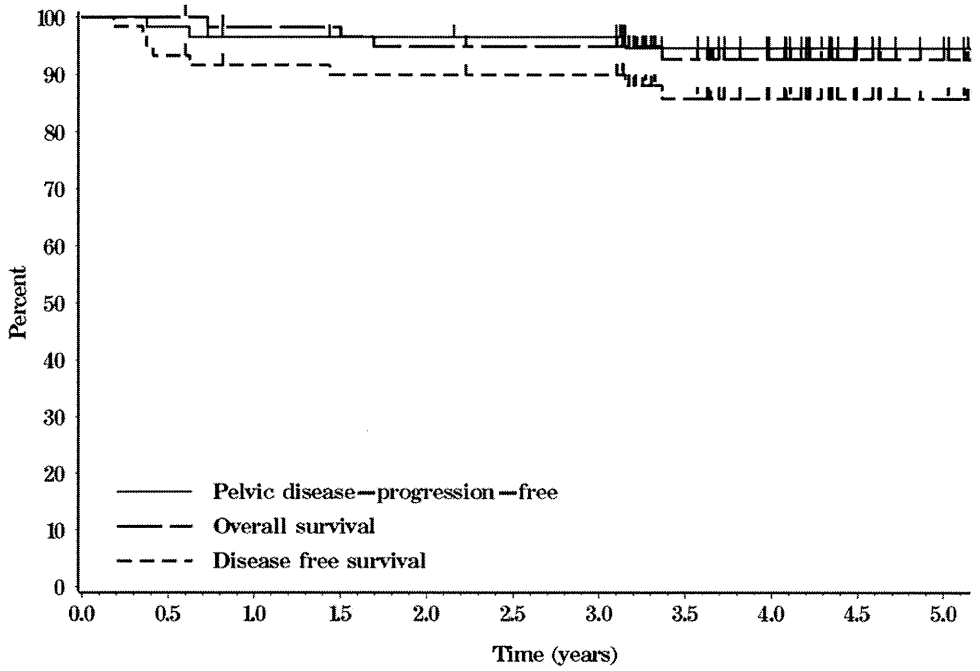

Fig. 2. PDPF survival, OS, and DFS are shown for patients treated with definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED 62 Gy_{10} at point A).

As Petereit and Pearcey (23) claimed, 52 Gy is the minimum dose for eradicating subclinical microscopic disease (*i.e.*, low risk clinical target volume). However, in the definitive radiotherapy for cervical cancer, the dose distribution of ICBT with a steep dose gradient should be taken into account in analyzing dose response on local control. In some patients with small volume tumor, the minimum dose delivered to the tumor might be higher than a prescribed point A dose.

In addition to radiation physics issues, radiobiological parameters need to be taken into account to explain the favorable local control results, despite the low radiation dose delivered in our study. One potentially significant parameter is the short OTT in our study. The OTT has been reported to be one of the most important treatment factors affecting local control of cervical cancer (34). In our study, the relatively short median OTT (median, 43 days) might have positively affected the local control results. Fowler and colleagues (35) proposed a linear quadratic formula that takes time factors in account. Several investigators have demonstrated that the repopulation rate of cervical cancer cells increases at around 21 to 28 days after starting EBRT (36). Our treatment protocol specified that HDR-ICBT was to start at 2 to 3 weeks. Additionally, tumor cell heterogeneity in radiosensitivity and tumor volume have been implicated as important factors affecting tumor control probability in sophisticated radiobiological models (37). In our series, no patients with small tumors (<2–3 cm) developed local recurrence. This finding is supportive of the hypothesis that a lower dose might be sufficient for eradicating cancer cells in small volume tumors,

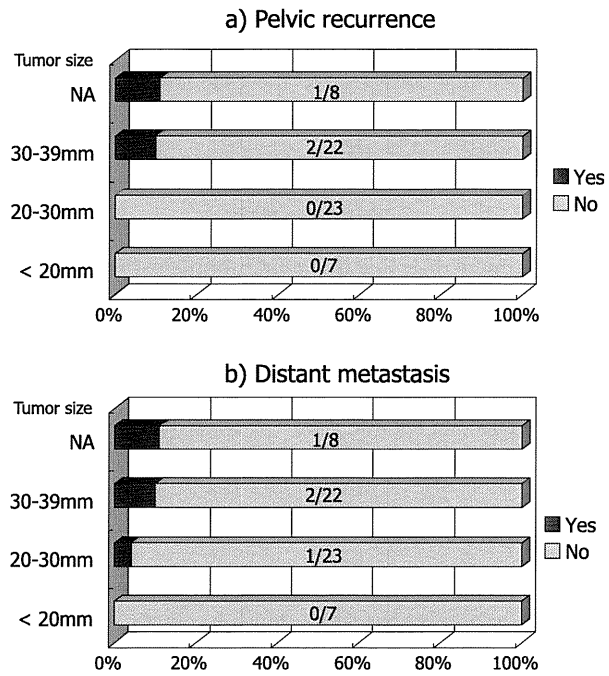

Fig. 3. Recurrence rate as a function of tumor size is shown for (a) pelvic recurrence and (b) distant metastasis. NA = not assessed (invisible on MRI).

Table 4. Late toxicities

Toxicity	No. of patients by toxicity grade (n = 60)			
	Grade 1	Grade 2	Grade 3	Grade 4
Small intestine	3	1	0	0
Large intestine/rectum	9	2	0	0
Bladder	0	1	0	0

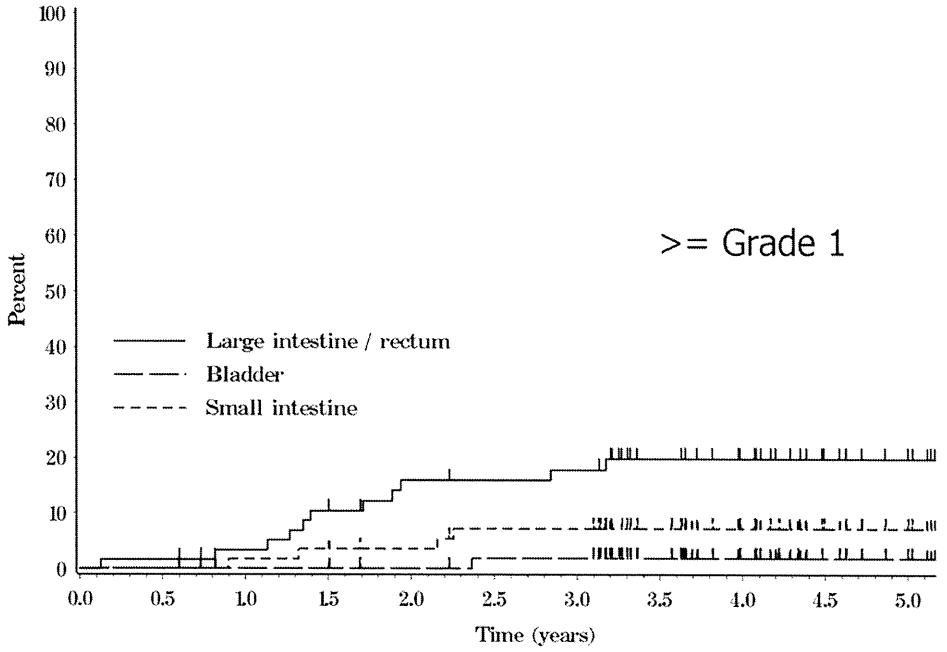

Fig. 4. Late complications (Grade ≥1) are shown for patients treated with definitive radiotherapy using HDR-ICBT with a low cumulative dose schedule (BED 62 Gy_{10} at point A).

even if such a low dose is not effective in treating bulky tumors.

In our study, acute and late toxicities were also evaluated prospectively. We assessed the incidence and grade of acute toxicities among our study patients as acceptable. Regarding late toxicities, no patient suffered severe gastrointestinal or genitourinary complications (Grade ≥3). We would consider this outcome to be a positive consequence of the low cumulative doses delivered to the central pelvis.

One potential limitation to our study was that the application of a MB might have introduced some degree of uncertainty with respect to the EBRT dose to the cervical tumor (38). This uncertainty resulted from the difficulty in confirming that the MB completely covered the cervix in every patient during every EBRT fraction in this study. Recently, onboard CT images have now become routinely available in clinical practice. Daily confirmation with this imaging device is feasible to confirm that an MB completely covers the cervical lesion.

CONCLUSIONS

In conclusion, the results of our study suggest that definitive radiotherapy consisting of whole-pelvis EBRT of 20 Gy/10 fractions, pelvic EBRT with an MB of 30 Gy/15 fractions, and HDR-ICBT of 24 Gy/4 fractions at point A (BED 62 Gy_{10}) is an effective and safe treatment for stage I and II cervical cancer patients with small (<4-cm) tumor diameter. Recently, the value of dose-volume histogram parameters for predicting local control in MR image-guided BT has been investigated for treating cervical cancer (39, 40). A future prospective study with the novel image-guided BT method using appropriate dose-volume histogram parameters is encouraged to confirm the findings of the present study in the near future.

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Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. 250–255, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.10.030

CLINICAL INVESTIGATION **Gynecologic Cancer**

INTERNATIONAL BRACHYTHERAPY PRACTICE PATTERNS: A SURVEY OF THE GYNECOLOGIC CANCER INTERGROUP (GCIG)

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Purpose: To determine current practice patterns with regard to gynecologic high-dose-rate (HDR) brachytherapy among international members of the Gynecologic Cancer Intergroup (GCIG) in Japan/Korea (Asia), Australia/New Zealand (ANZ), Europe (E), and North America (NAm).

Methods and Materials: A 32-item survey was developed requesting information on brachytherapy practice patterns and standard management for Stage IB–IVA cervical cancer. The chair of each GCIG member cooperative group selected radiation oncology members to receive the survey.

Results: A total of 72 responses were analyzed; 61 respondents (85%) used HDR. The three most common HDR brachytherapy fractionation regimens for Stage IB–IIA patients were 6 Gy for five fractions (18%), 6 Gy for four fractions (15%), and 7 Gy for three fractions (11%); for Stage IIB–IVA patients they were 6 Gy for five fractions (19%), 7 Gy for four fractions (8%), and 7 Gy for three fractions (8%). Overall, the mean combined external-beam and brachytherapy equivalent dose (EQD2) was 81.1 (standard deviation [SD] 10.16). The mean EQD2 recommended for Stage IB–IIA patients was 78.9 Gy (SD 10.7) and for Stage IIB–IVA was 83.3 Gy (SD 11.2) ($p = 0.02$). By region, the mean combined EQD2 was as follows: Asia, 71.2 Gy (SD 12.65); ANZ, 81.18 (SD 4.96); E, 83.24 (SD 10.75); and NAm, 81.66 (SD, 6.05; $p = 0.02$ for Asia vs. other regions).The ratio of brachytherapy to total prescribed dose was significantly higher for Japan ($p = 0.0002$).

Conclusion: Although fractionation patterns may vary, the overall mean doses administered for cervical cancer are similar in Australia/New Zealand, Europe, and North America, with practitioners in Japan administering a significantly lower external-beam dose but higher brachytherapy dose to the cervix. Given common goals, standardization should be possible in future clinical trials. © **2012 Elsevier Inc.**

Brachytherapy, Cervical cancer, Radiation dose.

INTRODUCTION

Globally, cervical cancer represents the most common gynecologic malignancy (1). Patients with locally advanced cervical cancer (Stage IB2–IVA) require treatment with external-beam radiation (EBRT) with concurrent chemotherapy administered as a radiation sensitizer followed by brachytherapy (2). The recommended cumulative dose of EBRT and brachytherapy to cure locally advanced disease

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Presented at the Cervical Cancer State of the Science Meeting, Manchester, UK, June 18, 2009.

Supplementary material for this article can be found at www.redjournal.org.

Conflict of interest: none.

Acknowledgment—The authors thank Barbara Silver for reviewing the manuscript and the physician respondents to this survey.

Received July 3, 2010, and in revised form Sept 3, 2010. Accepted for publication Oct 6, 2010.

ranges from 80 to 90 Gy recorded at point A using low-dose-rate (LDR) brachytherapy (2).

Over the past 20 years, high-dose-rate (HDR) brachytherapy has increased and replaced LDR in many practices (3). The Patterns of Care for cervical cancer radiation practice in the United States reported a 16% HDR utilization rate in 1999 (4), whereas 85% of surveyed physician members of the American Brachytherapy Society (ABS) reported having HDR at their institution in 2007 (3). Overall, randomized studies indicate that outcomes with HDR resemble those with LDR, though many issues exist regarding the methodology of randomization and the follow-up duration across the studies (5). However, caution regarding large fractions given to normal tissues and adequate tumor coverage have increased awareness and recommendations for the use of computed tomography (CT) or magnetic resonance imaging (MRI) to determine doses to the tumor and the organs at risk (6).

The biologic equivalent dose formulas allow calculation of the brachytherapy dose (7, 8). However, these formulas require an assumption that the α/β ratio for tumor is 10, which may be an underestimation for squamous cell carcinoma. Furthermore, concerns regarding the validity of the linear quadratic model exist for very low or very high doses per fraction (9). Publication of standard fractionation regimens for HDR cervical cancer brachytherapy with point A–based standard loading (10, 11) led to widespread adoption in the United States of the regimen 6 Gy for five fractions over approximately 2.5 weeks. Preliminary results demonstrate a 2-year Grades 3 and 4 bowel toxicity rate of 11% with this HDR regimen (12). By contrast, with 2-year follow-up, only three (5%) Grade 3 or greater gastrointestinal complications occurred in a group of 65 patients treated with 6 Gy for five fractions in one report (13). It remains unknown whether 6 Gy for five fractions has a higher toxicity rate than 5.5 Gy per fraction or than LDR brachytherapy.

The Gynecologic Cancer Intergroup (GCIG) strives to forge collaborations between cooperative groups to move the development of oncologic clinical trials forward in a highly constructive and cost-effective manner. Randomized trials with international participation will accrue cervical cancer patients rapidly and result in advances on a global stage. To determine brachytherapy practice patterns and the HDR brachytherapy regimens most frequently prescribed by GCIG members, a survey of GCIG members was conducted. The goal is to clarify which regimen would be acceptable for future international collaborative clinical trials.

METHODS AND MATERIALS

The GCIG represents an international association of member cooperative groups conducting large clinical trials for gynecologic malignancies. Since its inception in 1997, 18 cooperative groups have joined, including the AGO-Austria (Austria), AGO-OVAR (Germany), ACRIN (USA), ANZOG (Australia, New Zealand), DGOG (the Netherlands), EORTC (Europe), GEICO (Spain), GINECO (France), GOG (USA), JGOG (Japan), MANGO (Italy), MITO (Italy), MRC/NCRI (Great Britain), NCIC (Canada), NSGO (Scandinavia), RTOG (USA), SGCTC (Scotland), and SWOG (USA).

A 32-question survey was designed to address questions regarding standard practice patterns for locally advanced cervical cancer management, such as routine doses of external beam and the use of concurrent chemotherapy, and also to determine baseline brachytherapy practice patterns, including both HDR and LDR utilization, at the time of the survey (Appendix EI available online at at www.redjournal.org). An e-mail providing background information, the purpose of the survey, and a link to a web page for easy retrieval of the survey was sent electronically to the chair of each GCIG member cooperative group in December 2008. Each cooperative group chair could choose to forward the email to six radiation oncology members from separate representative centers that had a large volume of cervical cancer cases. Respondents could complete only one survey on a computer, and entered their names and e-mail addresses to avoid duplicate submissions. The survey website closed in May 2009. Appendix E1 (available online at at www.redjournal.org) lists the specific items queried.

The biologically equivalent doses were calculated in 2-Gy equivalents using the EQD2 equation. For respondents that used a midline block, the total dose to the nodes and the dose to the cervix were summed separately. The EBRT and brachytherapy EQD2 doses were calculated at point A for patients with Stage IB–IIA and those with Stage IIB-IVA disease; then the average was taken for a cumulative sum for all stages. Analysis of reported HDR fractionation regimens was divided by country and by region, including Asia (Japan/Korea); Australia/New Zealand; Europe (Austria, Denmark, England, Finland, Germany, Italy, Ireland, the Netherlands, Scotland, Spain); and North America (USA, Canada). Quartiles of dose were evaluated to determine whether any particular region or country grouped into the highest or lowest dose ranges. The *t*-test statistic was performed to determine whether any significant differences in dose existed by region.

RESULTS

Respondent characteristics

A total of 16 cooperative groups gave member responses to this survey. Of 74 respondents, two were excluded: one non-GCIG member and one GCIG member who did not answer questions regarding brachytherapy, yielding a final study population of 72 respondents. Cooperation was received from the AGO-Austria (n = 3), ABO-Germany (n = 2), ACRIN (n = 1), ANZGOG (n = 6), DGOG (n = 6), EORTC (n = 5), GEICO (n = 1), GOG (n = 5), JGOG (n = 6), KGOG (n = 4), MANGO (n = 3), MITO (n = 2), MRC/NCRI (n = 9), NCIC (n = 10), NSGO (n = 3), and the RTOG (n = 6). Regions of the world represented were Japan/Korea (n = 10), Australia/New Zealand (n = 6), Europe (n = 34), and North America (n = 22).

Of the 72 respondents, 63 (88%) practice radiation oncology; 8 (11%), both medical and radiation oncology; and one (1%), gynecologic oncology. Regarding the average number of cervical cancer patients treated per year, 7 (10%) treat 1 to 9, 18 (25%) treat 10 to 19, 11 (15%) treat 20 to 29, 9 (13%) treat 30 to 39, 6 (8%) treat 40 to 49, 10 (14%) treat 50 to 59, 6 (8%) treat 60 to 69, 4 (6%) treat 70 to 79, and 1 (1%) treats more than 140.

External-beam radiation to the cervix

Physicians were queried regarding the standard EBRT dose prescribed for treating cervical cancer. For those who reported administering a parametrial boost dose, the parametrial doses were excluded from the EBRT cumulative cervical dose calculation, since the goal of a midline block is to avoid significant radiation to the cervix during these fractions. After averaging all respondents' reported dose to the cervix, the mean EBRT dose was 44.2 Gy (range, 19.8–50.4) for Stage IB–IIA patients and 47.2 Gy (range, 30.6–54) for Stage IIB–IVA patients. The average cervical dose for the Japanese respondents (not including the parametrial boost dose) was 23.3 Gy (range, 19.8–30) for Stage IB-IIA patients and 36.7 Gy (range, 30.9–40) for Stage IIB–IVA patients. All Japanese respondents commented that after insertion of a midline block, the total dose to the parametria and pelvic nodes equals 50 Gy (30 Gy to the cervix plus 20 Gy after insertion of the midline block). By contrast, all other countries reported a mean EBRT dose of 46.11 Gy (range, 40–50.4) for Stage IB–IIA patients and 48.2 Gy (range, 40–54) for Stage IIB–IVA patients. The most commonly added parametrial boost dose is 5.4 Gy after 45 Gy to the entire pelvis. For Stage IB–IIA patients, the most common EBRT doses are 45 Gy (n = 41, 57%) and 50.4 Gy (n = 15, 21%). For Stage IIB–IVA, the most common EBRT doses are 45 Gy (n = 26, 36%), 50.4 Gy (n = 27, 38%), and 54 Gy (n = 5, 7%).

All respondents prescribe concurrent chemotherapy with EBRT. In addition, 4% (three respondents) consider giving neoadjuvant chemotherapy before concurrent chemoradiation. The chemotherapy agents marked on the survey included cisplatin (97%), 5-flourouracil (4%), carboplatin (5%), paclitaxel (5%), and nedaplatin (2%).

Brachytherapy

With regard to dose rate, 61 respondents (85%) have HDR available, 13 (18%) had LDR, and 8 (11%) have pulse-dose-rate. Chemotherapy is given on the same day as an HDR fraction by four respondents (6%). An HDR fraction is given on the same day as an EBRT fraction by three respondents (4%). A total of 38% of respondents might hospitalize patients overnight for HDR treatment. For those using LDR, an equal number of respondents use on average one or two fractions, with a per-fraction dose ranging from 10 to 40 Gy. Three respondents administer chemotherapy during an inpatient LDR hospitalization.

The tandem and ovoid is the most frequently used applicator for HDR, pulse-dose-rate, and LDR, with 54% using this applicator for more than 75% of their cases annually. The tandem and ring applicator is used in 24% of cases, tandem and cylinder in 4%, tandem and interstitial in 3%, and interstitial only in 1%. For applicator insertion, 97% of respondents' patients receive anesthesia, consisting of general (46%), spinal (27%), intravenous conscious sedation (28%), and/or oral pain medication (14%). Ultrasound is used for assistance with applicator insertion by 62% of respondents; 24% use ultrasound less than 10% of the time, 12% use it for 10–25% of cases, 7% use it for 26–50% of cases, 1% use it for 51–75% of cases, and 18% use it for more than 75% of their cases.

With regard to imaging the brachytherapy applicator after insertion, 17 centers (24%) reported that they use plain x-ray films, either alone or in combination with MRI and/or CT. By contrast, CT is the most commonly used imaging modality (n = 41, 57%); 27 respondents use CT for every fraction, and 14 use CT for the first fraction only. MRI is used by 18 centers (25%), of which eight use MRI for every fraction and 10 for the first fraction only; of these 10, eight acquire a CT scan for every fraction. In terms of prescribing to the cervix, 56 (78%) prescribe to point A, 8 (11%) follow the GEC-ESTRO guidelines (14, 15) alone, 15 (21%) follow the GEC-ESTRO and report dose to point A, 4 (6%) follow the ABS guidelines alone, and 8 (11%) use both the ABS and point A.

The major HDR fractionation patterns are depicted in Fig. 1 and listed in the table. For Stage IB–IIA patients, the most common HDR fractionation pattern is 6 Gy for five fractions (n = 11, 15%), as it is for Stage IIB–IVA patients (n = 14, 19%). A total of 28 fractionation regimens are reported, of which 18 are used by only one institution. The most common fractionation regimen, 6 Gy for five fractions, is prescribed by centers in the United States, Canada, Australia, New Zealand, the United Kingdom, Spain, Italy, and Germany. The second most common regimen, 7 Gy for four fractions, is prescribed by centers in the United States, Australia, Austria, and the Netherlands. For HDR dose reporting, of the 68 respondents to this question, 32 (47%) calculate equivalent dose using the 2-Gy (EQD2) formula, whereas 31 (46%) use only the biologic equivalent dose formula, and five (7%) multiply the raw cumulative dose by 1.33.

The recommended mean combined EBRT plus brachytherapy EQD2 was 78.9 Gy (standard deviation [SD] 10.7) for Stage IB–IIA patients and 83.3 Gy (SD 11.2) for Stage IIB–IVA patients for all countries (p = 0.02 Stage IB–IIA vs. IIB–IVA). For all stages and all countries, the mean EBRT plus brachytherapy dose was 80.9 (SD 10.14). By region, the mean combined EQD2 for Australia/New Zealand was 81.18 (SD 4.96); for Europe, 83.35 (SD 10.75); for North America, 81.66 (SD 6.05); and for Asia, 71.2 Gy (SD 12.65; p = 0.02 for Asia vs. other regions). The mean EBRT plus brachytherapy dose for Japan was 62.73 (SD 6.7), and for Korea it was 83.9 (SD 6.86). Therefore, the only significant difference was between Japan and the other countries in the survey. Overall, 17 centers (7 Europe, 3 North America, 6 Japan, and 1 New Zealand) had EQD2 cumulative values ranging from 56.8 to 75 Gy; 6 centers (all in Europe) reported EQD2 values over 95 Gy, ranging from 97.6 to 115.4 Gy. The highest reported dose was from a center that uses a fractionation regimen of 7 Gy for seven fractions after full-dose radiation to the pelvis. Figure 2 depicts the EQD2 by region.

The average ratio of brachytherapy dose to total sum (EBRT plus brachytherapy) dose was 0.45 (SD 0.08) for Stage IB–IIA and 0.44 (SD 0.08) for Stage IIB–IVA (p = NS). However, for Japanese respondents, the all-stages ratio