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International Brachytherapy Practice Patterns: A Survey of the Gynecologic Cancer Intergroup (GCIG)

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Abstract

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 (NA).

Materials and Methods—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%) utilized HDR. The three most common HDR brachytherapy fractionation regimens for Stage IB-IIA patients were 6 Gy for 5 fractions (18%), 6 Gy × 4 (15%), 7 Gy × 3 (11%), and for Stage IIB-IVA patients were 6 Gy for 5 fractions (19%), 7 Gy × 4 (8%), and 7 Gy × 3 (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: Asia, 71.2 Gy (SD,

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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 dose administered for cervical cancer is 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.

Keywords

brachytherapy; cervical cancer; radiation dose

Introduction

Globally, cervical cancer represents the most common gynecologic malignancy in women.¹ Patients with locally advanced cervical cancer (stage IB2-IVA) require management with external-beam radiation (EBRT) with concurrent chemotherapy administered as a radiation sensitizer followed by brachytherapy (BT).² The recommended cumulative dose of EBRT and BT to cure locally advanced disease ranges from 80–90 Gy recorded at point A using low-dose-rate (LDR) BT.²

Over the past 20 years, high-dose-rate (HDR) BT use has increased and replaced LDR in many practices.³ The Patterns of Care for cervical cancer radiation practice in the U.S. 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 regarding the methodology of randomization and the follow-up duration across the studies exist.⁵ However, caution regarding large fractions given to normal tissues and adequate tumor coverage have increased awareness and recommendations for the use of CT or MRI imaging to determine doses to the tumor and the organs at risk.⁶

The biologic equivalent dose formulas allow calculation of the BT dose.^{7, 8} However, these formulas require an assumption that the α/β ratio for tumor is 10, which may be an underestimate for squamous cell carcinoma. Furthermore, concerns regarding the validity of the LQ model exist for very low or very high doses per fraction.⁹ Publication of standard fractionation regimens for HDR cervical-cancer BT with point A based standard loading^{10, 11} led to widespread adoption in the U.S. of the regimen 6 Gy for 5 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 In contrast, with 2-year follow-up only 3 (5%) grade 3 or greater GI complications occurred in a group of 65 patients treated with 6 Gy for 5 fractions at the University of Utah.¹³ Whether 6 Gy for 5 fractions has a higher toxicity rate than 5.5 Gy per fraction or than LDR BT, remains unknown.

The Gynecologic Cancer Intergroup (GCIG) strives to forge collaborations between cooperative groups in order to move oncologic clinical-trial development 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. In order to determine brachytherapy practice patterns and the HDR brachytherapy regimens most frequently prescribed by GCIG members, a survey of GCIG members was conducted. It is hoped that this will clarify which regimen would be acceptable for future international collaborative clinical trials.

Materials and Methods

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, as well as to determine baseline BT practice patterns, including both HDR and LDR utilization, at the time of the survey (Appendix eI). An email 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 6 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 email addresses to avoid duplicate submissions. The survey website closed in May, 2009. Appendix 1 lists the specific items queried.

The biologically equivalent doses were calculated in 2-Gy equivalents using the EQD2 equation. The dose per fraction from BT, when combined EBRT, was normalized to 2 Gy/fraction using the linear quadratic model with an $\alpha/\beta=10$ for tumor. The biologically weighted dose in equivalent 2 Gy fractions with an $\alpha/\beta=10$ formula is:

$$Nd(1+d)/\alpha/\beta \div 1.2 \quad \text{Equation 1}$$

where n is the number of fractions, d equals the dose per fraction, and $\alpha/\beta=10$. EBRT and BT EQD2 doses were calculated at point A for patients with Stage IB-IIA and those with Stage IIB-IVA disease, then the average 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 had member response to this survey. Of 74 respondents, 2 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 1-9, 18 (25%) treat 10-19, 11 (15%) treat 20-29, 9 (13%) treat 30-39, 6 (8%) treat 40-49, 10 (14%) treat 50-59, 6 (8%) treat 60-69, 4 (6%) treat 70-79 and 1 (1%) treats >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 assuming for calculation purpose that the cervix does not receive a significant amount of radiation during these fractions. After averaging all respondents' reported dose to the cervix, the mean EBRT dose is 44.2 Gy (range [rg], 19.8–50.4) for Stage IB-IIA patients and is 47.2 Gy for Stage IIB-IVA patients (rg, 30.6–54). The average cervical dose for the Japanese respondents (not including the parametrial boost dose) is 23.3 Gy (rg, 19.8–30) for Stage IB-IIA and is 36.7 Gy (rg, 30.9–40) for Stage IIB-IVA. All Japanese respondents commented that after inserting a midline block the total dose to the parametria and pelvic nodes equals 50 Gy (30 Gy to the cervix plus 20 Gy after the midline block is inserted). In contrast, all other countries reported a mean EBRT dose of 46.11 Gy (rg, 40–50.4) for Stage IB-IIA and 48.2 Gy (rg, 40–54) for Stage IIB-IVA. 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% (3 respondents) consider neoadjuvant chemotherapy prior to concurrent chemo-radiation. The chemotherapy agents marked on the survey included cisplatin (97%), 5-fluorouracil (4%), carboplatin (5%), paclitaxel (5%), and nedaplatin (2%).

Brachytherapy

With regard to dose rate, 61 respondents (85%) have HDR available, 13 (18%) have LDR, and 8 (11%) have pulse-dose-rate (PDR). Chemotherapy is given on the same day as an HDR fraction by 4 respondents (6%). An HDR fraction is given on the same day as an EBRT fraction by 3 respondents (4%). A total of 38% of respondents may 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 10–40 Gy. Three respondents administer chemotherapy during an inpatient LDR hospitalization.

The tandem and ovoid is the most frequently used applicator for HDR, PDR 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, the 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%), IV 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 >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. In 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 8 use MRI for every fraction, and 10 for the first fraction only; of these 10, 8 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 Figure 1 and listed in Table 1. For Stage IB-IIA patients, the most common HDR fractionation patterns was 6 Gy for 5 fractions (n=11, 15%), as it was for Stage IIB-IVA patients (n=14, 19%). A total of 28 fractionation regimens were reported, of which 18 were used by only one institution. The most common fractionation regimen, 6 Gy $\times$ 5 fractions, is prescribed by centers in the USA, Canada, Australia, New Zealand, the UK, Spain, Italy and Germany. The second most common regimen, 7 Gy $\times$ 4, is prescribed by centers in the USA, 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 BED formula, and 5 (7%) multiply the raw cumulative dose by 1.33.

The recommended mean combined EBRT+BT EQD2 is 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 versus IIB-IVA). For all stages and all countries, the mean EBRT+BT dose is 80.9 (SD, 10.14). By region, the mean combined EQD2 for Australia/New Zealand is 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+BT dose for Japan is 62.73 (SD, 6.7) and for Korea it is 83.9 (SD, 6.86). Therefore, the only significant difference is between Japan and the other countries in the survey. Overall, 17 centers (7 Europe, 3 North America, 6 Japan, 1 New Zealand) have EQD2 cumulative values ranging from 56.8 to 75 Gy; 6 centers (all in Europe) report EQD2 values over 95 Gy, ranging from 97.6 to 115.4 Gy. The highest reported dose is from a center that utilizes a fractionation regimen of 7 Gy for 7 fractions after full-dose radiation to the pelvis. Figure 2 depicts the EQD2 by region.

The average ratio of BT dose to total sum (EB + BT) dose is 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 is 0.51 (SD, 0.03) which is significantly different from the average ratio for all other countries ($p=0.0002$). When stratified by stage, this difference in BT ratio is only seen for the Stage IB-IIA sub-group. For Japanese respondents, the ratio of BT:EB+BT is 0.58 (SD, 0.05) for Stage IB-IIA and 0.45 (SD, 0.06) for Stage IIB-IVA ($p=0.002$). In other words, to accommodate their reduced EBRT dose, the Japanese use a higher BT dose for patients with Stage I-IIA tumors than is typically used elsewhere.

Complications

When queried about the number of patients treated for cervical cancer who were hospitalized annually for a complication, most respondents indicated 0 (n=12, 17%), 1 (n=37, 60%), or 2 (n=9, 13%).

Discussion

The primary goal of this survey was to gauge variation in HDR fractionation for cervical cancer and to determine BT practice patterns internationally, in order to assist with the development of the BT portion of international randomized clinical trials. As cervical cancer remains a leading cause of mortality in developing countries, the need for international collaborative randomized trials that can advance treatment approaches on a global level are needed. In particular, prior to this study, we questioned whether the heterogeneity of BT practice might hinder standardization. As part of this survey, other items of interest were queried, including the utilization of 3D imaging during BT. Other questions were designed

to provide a 3-year update to selected general management information queried on the 2007 survey.¹⁶

With regard to the general management of cervical cancer, this survey showed that the use of concurrent chemo-RT is similar to that reported in the 2007 survey, as are EBRT doses. In terms of BT, a greater proportion of respondents in this survey reported the use of HDR than in a U.S.-based survey from 1999.⁴ However, use of HDR in the U.S. also appears to be increasing, with 85% of ABS members having HDR BT available in their practices in 2007, indicating a growing acceptance of HDR BT in the U.S. that matches international implementation.³ The transition from LDR to HDR has been based on an increased acceptance in the feasibility, safety and efficacy of HDR when carefully administered, with a concomitant increase in the use of 3D imaging. 3D imaging allows dose optimization away from the normal tissues in an attempt to spare them the large fractional dose used in HDR brachytherapy.

Overall, a significant proportion of GCIG members have access to 3-D imaging for gynecologic BT. CT is the most frequently used method for BT imaging. In a recent ABS survey, 70% of respondents used CT after BT applicator insertion, and 57% use CT imaging in this survey.³ Prior to 1990s plain x-ray film simulation was the standard of care. After the integration of CT into radiation oncology departments, 3D imaging use increased and now represents the standard for external beam. The integration of 3D imaging into brachytherapy has also expanded, albeit later than for external beam radiation. This study found a significant proportion utilizing the best available 3D imaging modality available at their institution, either CT or MRI, for cervical cancer brachytherapy planning.

In this survey, HDR BT dose fractionation recommendations varied considerably. The most common fractionation internationally was 6 Gy $\times$ 5 fractions, although this regimen was used by less than 20% of reporting institutions. Despite the high degree of individuality in BT prescribing, the biologic equivalence was remarkably similar for all countries and regions except Japan. All six Japanese respondents followed a regimen of treating to 20–30 Gy then placing a midline block, which significantly reduced the cumulative EQD2 cervical dose compared to that used in other countries. Nevertheless, the EQD2 dose to the cervix was equivalent, on average 80 Gy for all regions of the world surveyed. The Japanese cervix dose reduction to approximately 70 Gy, instead of the international standard of 80 Gy, must be further analyzed, including comparison of recurrence rates and toxicities; an upcoming abstract shows reasonable rates of local control.¹⁷ The Japanese regimen, in use for several decades, was implemented upon the observation that Japanese women, potentially due to their small body size, had very high bowel and bladder toxicity rates when treated with higher pelvic EB doses.¹⁸ The current Japanese regimen begins HDR intracavitary brachytherapy once per week after 20 Gy. Whether a genetic difference in sensitivity to radiation exists is unknown, but one implication of the successful outcomes of Japanese women is that BT may be the more critical component for treatment to the cervix.

A previously un-assessed difference in brachytherapy administration was identified with regard to the proportional relationship of brachytherapy to the sum total dose. For early-stage patients, the Japanese respondents administer a significantly higher proportion of the dose using brachytherapy than do practitioners from other countries. The reliance on HDR brachytherapy fractionation may indicate that a large dose given with HDR can compensate for a lower external beam dose in patients with small tumors. This assumption of proportionality must be corroborated with recurrence information.

For all respondents (including those from Japan) the mean EBRT+B cumulative EQD2 dose was 80.4 Gy with a standard deviation of 10 Gy. Patients with a higher stage (IIB-IVA)

received a significantly higher dose than those with earlier stage cervical cancer. Therefore, a dose of 80 Gy may be considered the universally accepted international baseline dose overall, with on average 79 Gy for Stage IB-IIA and 84 Gy for Stage IIB-IVA cases. A dose of 80 Gy is approximately equivalent to 45 Gy delivered with EBRT and 5.5 Gy for 5 fractions delivered with HDR brachytherapy. A dose of 84 Gy is approximately equivalent to 45 Gy with EBRT and 6 Gy for 5 fractions or 7 Gy for 4 fractions of HDR.

Standardization of HDR BT on an international level will assist institutions in terms of comparing toxicities and outcomes for patients with cervical cancer, and will also allow for the exchange of information and uniformity in a multi-institutional international randomized clinical trial that permits HDR BT. A cumulative dose of 80 Gy should be considered an achievable goal for patients with locally advanced cervical cancer. Analysis of the outcomes of Japanese patients treated with a lower total dose is necessary. Future randomized trials in the era of chemo-radiation may attempt radiation dose variation based on response as well as improved normal-tissue sparing with 3D imaging, in order to determine the acceptable safe threshold level which results in equivalent eradication of disease while minimizing toxicities.

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Figure 1A.

Figure 1B.

Figure 1.

Cervical cancer HDR brachytherapy fractionation patterns by dose in Gray (Gy) and number of brachytherapy fractions prescribed. A) illustrates respondents answers regarding the fractionation pattern prescribed for Stages IB-IIA cervical cancer. B) illustrates the fractionation pattern recommended for Stages IIB-IVA cervical cancer. The size of the circle is proportional to the number of respondents, with the largest number reporting 6 Gy × 5 fractions.

Figure 2.

The sum external beam plus brachytherapy dose with the error bars indicating the standard deviation (SD), converted using the equivalent dose in 2-Gy fractions (EQD2) assuming an $\alpha/\beta=10$, by region of the world. The mean EQD2 dose was 80.9 Gy (SD 10.14).

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Table 1

GCIG physicians that use HDR brachytherapy for cervical cancer were queried regarding the specific fractionation regimen that they routinely implement for stages IB-IIA and stages IIB-IVA cervical cancer patients. The results depict the diversity of responses. The EQD2 formula was used to convert the HDR dose and number of fractionations.

Standard Fractionation For Stages IB-IIA Cervical Ca			
% Respondents (#)	Dose/Fraction	# Fractions	EQD2
18% (11)	6	5	40
15% (9)	6	4	32
12% (7)	7	3	29.75
8% (5)	5	6	37.5
8% (5)	7	4	39.7
5% (3)	5	5	31.25
5% (3)	5.5	5	35.52
3% (2)	8	3	36
1.6% (1)	3	8	26
1.6% (1)	4	5	23.3
1.6% (1)	4	6	28
1.6% (1)	5	3	18.75
1.6% (1)	5	4	25
1.6% (1)	5.5	3	21.3
1.6% (1)	6	3	24
1.6% (1)	6.5	4	35.75
1.6% (1)	7	5	49.6
1.6% (1)	7	6	59.5
1.6% (1)	7	7	69.4
1.6% (1)	7.5	2	21.9
1.6% (1)	8	2	24
1.6% (1)	8	4	48
1.6% (1)	8.5	2	26.2
1.6% (1)	10	3	50

Standard Fractionation For Stages IIB-IVA Cervical Ca				
% Respondents (#)	Dose/Fraction	# Fractions	EQD2	
23% (14)	6	5	40	
10% (6)	7	4	40	
10% (6)	7	3	30	
8% (5)	6	4	32	
7% (4)	5.5	5	35.5	
5% (3)	5	6	37.5	
5% (3)	7	6	59.5	
5% (3)	6	3	24	
5% (3)	8	3	36	
3% (2)	7	7	69.4	
3% (2)	5	5	31.3	
1.6% (1)	3	8	26	
1.6% (1)	4	6	28	
1.6% (1)	7	5	49.6	
1.6% (1)	8	4	48	
1.6% (1)	9	4	57	
1.6% (1)	5	3	18.8	
1.6% (1)	5.5	3	21.3	
1.6% (1)	5	2	12.5	
1.6% (1)	7.5	2	21.9	
1.6% (1)	8	2	24	
1.6% (1)	8.5	2	26.2	