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Clinical Investigation

Clinical Outcomes of Computed Tomography—Based Volumetric Brachytherapy Planning for Cervical Cancer



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Summary

Image guided brachytherapy (IGBT) has been adopted by multiple centers in recent years for the treatment of cervical cancer. The clinical outcomes are promising, with favorable results compared with those of conventional techniques. Previously reported studies have used primarily magnetic resonance imaging—based treatment planning. We report the clinical outcomes of a novel hybrid computed tomography—based IGBT technique. At 2 years, local control was excellent, with low rates of treatment toxicity. Further

Purpose/Objectives: A report of clinical outcomes of a computed tomography (CT)-based image guided brachytherapy (IGBT) technique for treatment of cervical cancer.

Methods and Materials: Seventy-six women with International Federation of Gynecology and Obstetrics stage IB to IVA cervical carcinoma diagnosed between 2007 and 2014 were treated with definitive external beam radiation therapy (EBRT) with or without concurrent chemotherapy followed by high-dose-rate (HDR) IGBT. All patients underwent planning CT simulation at each implantation. A high-risk clinical target volume (HRCTV) encompassing any visible tumor and the entire cervix was contoured on the simulation CT. When available, magnetic resonance imaging (MRI) was performed at implantation to assist with tumor delineation. The prescription dose was prescribed to the HRCTV.

Results: The median follow-up time was 17 months. Thirteen patients (17%) had an MRI done before brachytherapy, and 16 patients (21%) were treated without MRI guidance. The mean EBRT/IGBT sum 2-Gy equivalent dose (EQD2) delivered to the 90% volume of the HRCTV was 86.3 Gy. The mean maximum EQD2s delivered to 2 cm³ of the rectum, sigmoid, and bladder were 67.5 Gy, 66.2 Gy, and 75.3 Gy, respectively. The 2-year cumulative incidences of local, locoregional, and distant failure were 5.8% (95% confidence interval [CI]: 1.4%-14.8%), 15.1% (95% CI: 5.4%-29.4%), and 24.3% (95% CI: 12.1%-38.9%), respectively. The 2-year overall and disease-free survival rates were 75% (95% CI, 61%-91%) and 73% (95% CI, 60%-90%), respectively. Twenty-nine patients (38%) experienced grade ≥ 2 acute toxicity, with 5 cases of acute grade 3 toxicity and no grade ≥ 4 toxicities. One

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Conflict of interest: none.

follow-up is needed to evaluate the long-term outcomes of this technique.

patient experienced grade 3 gastrointestinal toxicity. No other late grade ≥ 3 events were observed.

Conclusions: This is the largest report to date of CT/MRI-based IGBT for the treatment of cervical cancer. The results are promising, with excellent local control and acceptable toxicity. Further investigation is needed to assess the long-term safety and efficacy of this treatment. © 2015 Elsevier Inc. All rights reserved.

Introduction

For decades, brachytherapy for cervical cancer has relied on conventional point-based techniques originally developed in the 1930s (1, 2). These conventional methods use 2-dimensional radiographs with dose prescribed to standard points that are meant to represent anatomic landmarks in the pelvis. This traditional method does not account for tumor and anatomic variations. As a result, point-based brachytherapy planning can underestimate tumor size and lead to underdosing and poor local control, especially in larger tumors (3, 4). Point dosing can also lead to excessive normal tissue toxicity, as with smaller tumors and smaller uteri in which predefined points may deliver dose into the bladder or rectum. Conventional International Commission on Radiation Units and Measurements (ICRU) points have been shown in several studies to underestimate maximum doses to the bladder and rectum (3, 5-11), and doses to these points have often failed to correlate with late toxicity (12). This may in part explain the relatively high rates of severe late gastrointestinal (GI) and genitourinary (GU) toxicity in the range of 5% to 10% reported in previous studies of conventional treatment techniques (13-16).

In recent years, the Groupe Européen de Curiethérapie/European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) working group has developed a magnetic resonance image (MRI)-guided volume-based brachytherapy technique that takes into account tumor extent at the time of diagnosis and brachytherapy (17, 18). The clinical outcomes are promising, with high rates of local control and low rates of GU and GI toxicity (19, 20). Furthermore, this work has resulted in the development of useful dose-volume histogram (DVH) parameters for tumor and normal tissues that correlate well with clinical outcomes (12, 21).

Although MRI-based IGBT is an attractive option with the potential to improve disease control and minimize late treatment toxicity, it relies on repeated MRIs done during treatment. For many radiation departments, the routine use of MRI at each brachytherapy fraction is not feasible because of its cost and inaccessibility. To address this issue, a few groups, including our own, have adopted a hybrid computed tomography (CT)-based IGBT technique (6, 22-24). When our department initially adopted this technique in 2007, MRI was routinely done for 1 brachytherapy fraction in all patients. However, owing to logistic issues, some patients are unable to undergo MRI at the time of brachytherapy, and thus we have adapted a solely

CT-based IGBT technique for these patients. The results of our 2-year clinical experience of CT-based IGBT with and without MRI are reported herein.

Methods

Patient population

Our Institutional Review Board approved this study. We included all patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB to IVA cervical cancer treated with definitive external beam radiation therapy (EBRT) with or without concurrent chemotherapy followed by image guided brachytherapy at our institution between 2007 and 2014. No patients had previously been treated with chemotherapy, radiation therapy, or both. Patients with metastatic disease at presentation were excluded.

EBRT planning

All patients underwent CT-based planning in the supine position with custom immobilization. The majority (93%) of patients were treated using intensity modulated radiation therapy (IMRT), and the remaining patients were treated with a 4-field 3-dimensional conformal technique. The clinical target volume (CTV) included the gross disease, cervix, parametria, uterus, superior third to half of the vagina, presacral region, and regional lymph nodes (common, internal and external iliacs). Inguinal nodes were treated in women with involvement of the inferior third of the vagina. Patients with clinical or pathologic evidence of disease in the para-aortic or superior common iliac nodes were treated with an extended-field technique. Planning margins of 15 mm around the cervix and uterus, 7 mm around the lymph nodes, and 10 mm around the remainder of the CTV were applied.

The IMRT plans consisted of 7 to 9 coplanar fields using 6-MV photons. The prescription dose to the planning target volume (PTV) ranged between 43.2 and 50.4 Gy (median, 45 Gy) in 24 to 28 fractions. IMRT planning constraints were as follows: (1) 95% of the PTV receives $>95\%$ of the prescription dose; (2) $<1\%$ of the PTV receives $<93\%$ of the prescription dose; (3) $<10\%$ of the PTV receives $>110\%$ of the prescription dose; and (4) maximum dose to the PTV $<120\%$ of the prescription dose. Normal tissue planning

objectives were as follows: (1) rectum: maximum dose <50 Gy; (2) bowel: volume receiving >45 Gy (V45) <250 cc; and (3) pelvic bone marrow (BM): volume receiving >20 Gy (V20) <75%, volume receiving >10 Gy (V10) <90%.

Patients with clinical evidence of nodal involvement received an external beam boost to gross nodal disease of 52.5 to 59.4 Gy using a simultaneous-integrated or sequential technique. Patients with parametrial or pelvic side wall involvement received a sequential boost to the parametria to 50.4 to 60 Gy by the use of anterior–posterior/posterior–anterior fields after brachytherapy.

Chemotherapy

The majority (95%) of patients received concurrent chemotherapy. Fifty-nine patients (78%) received weekly cisplatin (40 mg/m²), and 13 patients (17%) received combined cisplatin and gemcitabine as part of a phase 1 trial. The median number of chemotherapy cycles given was 5 (range, 1–6 cycles).

Brachytherapy

The majority of patients were treated with high-dose-rate (HDR) brachytherapy using a tandem-and-ovoid intracavitary device with an iridium-192 source. Five patients were treated

with tandem-and-cylinder devices because of vaginal involvement. One patient was treated with interstitial brachytherapy because of high-volume residual disease, and 3 patients were treated with interstitial brachytherapy because of difficult anatomy. A planning CT scan was obtained before the delivery of each fraction. The device position was confirmed at the time of each CT scan to ensure that the hub of the tandem was flush against the cervical os.

The high-risk clinical target volume (HRCTV) and organs at risk (OARs) were contoured on the planning CT according to the GEC-ESTRO guidelines (17, 18) using BrachyVision brachytherapy planning software (version 10.0; Varian Medical Systems, Palo Alto, CA). One of 3 radiation oncologists specializing in gynecologic malignancies contoured for each fraction. In most cases, all fractions for an individual patient were contoured by the same physician. The HRCTV included the entire cervix and visible residual gross tumor. An MRI was planned for the second fraction with the intracavitary device in place, because scheduling the MRI for the first fraction was infeasible. The HRCTV was then contoured on the fused T2-weighted axial MRI (Fig. 1). Points A were determined based on the flange of the tandem and moving superiorly 2 cm along the tandem and 2 cm perpendicular to the tandem in the lateral direction as outlined on the radiographs. The basis for treatment plans was initial prescription/normalization to point A. Dwell times were then

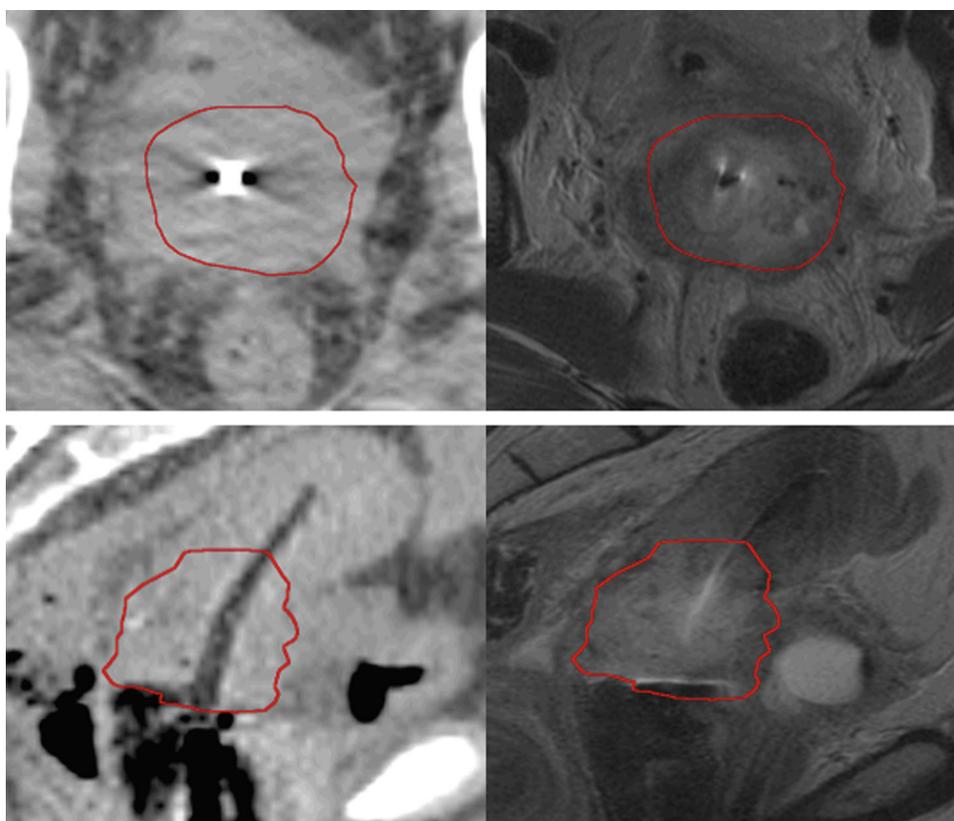


Fig. 1. Fused axial (above) and sagittal (below) brachytherapy planning simulation computed tomography (left) and magnetic resonance (right) images of high-risk clinical target volume (red). A color version of this figure is available at www.redjournal.org.

manually modified to maximize coverage of the HRCTV while reducing dose to the OARs. The prescription dose ranged from 25 to 30 Gy (median, 29 Gy) in 3 to 5 fractions. The most commonly used fractionation scheme was 27.5 to 30 Gy in 5 fractions, except for patients who were traveling long distances, for whom 4 fraction regimens were used. The DVHs were analyzed according to guidelines evaluating the ICRU 38 rectal and bladder points, point A, HRCTV, and the minimum 2-cc dose to the maximally irradiated rectum, sigmoid, and bladder.

The dose constraints for the HRCTV were to a D90 equal to the prescription dose, and the V100 of >90%. The doses to points A, B, and DVH parameters for HRCTV, rectal, sigmoid, and bladder were recorded. The brachytherapy dose was converted to the 2-Gy equivalent (EQD2) doses using the linear quadratic model ($\alpha/\beta = 10$ for HRCTV and $\alpha/\beta = 3$ for OARs). The total combined EBRT and brachytherapy doses were then calculated and recorded. An attempt was made to keep the maximum EQD2 doses to 2 cm³ (D2cc) of the rectum, sigmoid, and bladder below 75 Gy, 75 Gy, and 85 Gy, respectively.

Follow-up

Patients were followed up after treatment at 3- to 6-month intervals by their treating radiation oncologist and gynecologic oncologist. Follow-up evaluation included physical examination; abdominopelvic CT, positron emission tomography (PET)/CT, or both; Papanicolaou smears; blood counts; and chemistry profiles. A PET/CT was done 3 months after the end of treatment and yearly thereafter, unless symptoms dictated an earlier evaluation. Complete response was determined based on clinical examination and interpretation of PET and CT imaging by the multidisciplinary team including the radiation oncologist, radiologist, and gynecologic oncologist. Areas of suspicion on clinical examination or residual ¹⁸F-fluorodeoxyglucose uptake underwent biopsy. Patients were monitored during treatment for acute toxicity (up to 90 days after the start of treatment) and at each follow-up visit thereafter for late toxicities. Toxicity was graded by use of the Common Terminology Criteria for Adverse Events (version 3; ctep.cancer.gov). The highest grade of late GI and GU toxicity was reported for each patient.

Statistics

Survival outcome event times were measured from the time of diagnosis. Failure event times were measured from the start of treatment. Overall survival (OS) was defined as the time to death of any cause. Local failure, locoregional failure, and distant failure were defined as first radiographic or pathologic evidence of disease recurrence within or immediately adjacent to the HRCTV, the pelvis, or outside of the pelvis, respectively. Disease-free survival (DFS) was defined as the time to the first evidence of local failure,

locoregional failure, distant failure, or death of any cause. Patients not having a DFS event were censored at the last known medical encounter. Time to late toxicity was measured from the initiation of radiation therapy. We estimated OS and DFS outcomes using the Kaplan-Meier method (25). We estimated the incidence of local, locoregional, and distant failure using cumulative incidence functions (26). Each estimate was calculated separately; thus, a patient with 1 type of failure was capable of having a subsequent failure of another type. The same approach was used for calculating late toxicity. Statistical analyses were conducted with R version 2.15.1 (www.R-project.org; `cmprsk` package).

Results

Patient, tumor, and treatment characteristics

Seventy-six patients were evaluable. The patient and tumor characteristics are shown in Table 1. The median age of patients was 51 years. Forty-nine patients (64%) had FIGO stage IIB disease or greater. The majority (72%) of patients had squamous cell carcinoma. Twenty-six patients (34%) had radiographic evidence of pelvic or para-aortic nodal involvement at diagnosis. The treatment characteristics are shown in Table 2. The median treatment duration was 56 days. One patient had extended treatment duration because of noncompliance. As a result of logistic issues (primarily insurance coverage), only 47 patients (62%) had an MRI done at the time of brachytherapy. Thirteen patients (17%) had an MRI done before brachytherapy, and 16 patients (21%) were treated without MRI guidance. The mean difference in HRCTV volume between the first and second fractions for patients treated with and without MRI guidance were 1.0 cc (standard deviation [SD], ± 8.0 cc) and 3.5 cc (SD, ± 8.2 cc), respectively. The dosimetric parameters

Table 1 Patient and tumor characteristics (N=76)

Characteristic	n
Age, y, median (range)	51 (24-83)
Follow-up time, mo, median (range)	17 (3-54)
Histology, n (%)	
Squamous cell carcinoma	55 (72)
Adenocarcinoma	18 (24)
Other	3 (4)
FIGO stage, n (%)	
IB1	10 (13)
IB2	13 (17)
IIA	4 (5)
IIB	23 (30)
IIIA	1 (1)
IIIB	23 (30)
IVA	2 (3)

Abbreviation: FIGO = International Federation of Gynecology and Obstetrics.

Table 2 Treatment characteristics

Characteristic	n
Treatment duration, d, median (range)	56 (39-152)
EBRT dose, Gy, median (range)	45 (43.2-50.4)
EBRT technique, n (%)	
IMRT	71 (93)
3DCRT	5 (7)
Brachytherapy prescription dose, Gy, median (range)	29 (25-30)
V100 to HRCTV, %, median (range)	93.5 (75.2-99.7)
EBRT/IGBT EQD2 sum, Gy, mean (SD)	
HRCTV D90	86.3 (8.1)
Point A	79.0 (9.1)
Bladder D2cc	75.3 (9.2)
Rectum D2cc	67.5 (6.8)
Sigmoid colon D2cc	66.2 (7.9)
MRI guidance, n (%)	
Yes	60 (79)
No	16 (21)
Chemotherapy	
Cisplatin	59 (78)
Other	13 (17)
None	4 (5)
Cycles of chemotherapy, median (range)	5 (1-6)

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; D2cc = maximal dose to 2 cm³; D90 = dose to 90% of the volume; EBRT = external beam radiation therapy; EQD2 = equivalent dose in 2-Gy fractions; HRCTV = high-risk clinical target volume; IGBT = image guided brachytherapy; IMRT = intensity modulated radiation therapy; MRI = magnetic resonance imaging; V100 = percentage of volume receiving 100% of prescription dose.

for patients treated with and without MRI guidance are shown in [Table 3](#). The mean EBRT/IGBT sum EQD2 dose delivered to the 90% volume (D90) of the HRCTV was 86.3 Gy. The mean rectum, sigmoid, and bladder EQD2 doses delivered the D2cc were 67.5 Gy, 66.2 Gy, and 75.3 Gy, respectively.

Table 3 Dosimetric parameters for patients treated with or without MRI guidance

Factor	MRI guidance	No MRI guidance
V100 to HRCTV, mean (SD) (%)	93.6 (4.1)	91.6 (5.4)
EBRT/IGBT EQD2 sum, Gy, mean (SD)		
HRCTV D90	86.9 (9.0)	86.1 (7.0)
Bladder D2cc	73.3 (9.4)	78.3 (8.1)
Rectum D2cc	66.2 (6.8)	69.3 (6.5)
Sigmoid colon D2cc	65.9 (5.6)	66.9 (10.8)

Abbreviations: D2cc = maximal dose to 2 cm³; D90 = dose to 90% of the volume; EQD2 = equivalent dose in 2-Gy fractions; HRCTV = high-risk clinical target volume; MRI = magnetic resonance imaging; V100 = percentage of volume receiving 100% of prescription dose.

Outcomes

The median follow-up time was 17 months (range, 3-54 months). The 2-year cumulative incidences of local, locoregional, and distant failure were 5.8% (95% CI: 1.4%-14.8%), 15.1% (95% CI: 5.4%-29.4%), and 24.3% (95% CI: 12.1%-38.9%), respectively ([Fig. 2](#)). The 2-year rates of OS and DFS were 75% (95% CI, 61%-91%) and 70% (95% CI, 56%-86%), respectively ([Fig. 3](#)). Two patients had persistent disease that never resolved after chemoradiation, and 1 patient was found to have metastatic disease during the second week of treatment. The mean HRCTV volume at the time of the first brachytherapy implantation in patients with local failure, locoregional failure, and no locoregional failure were 64.3 cc (SD, ± 5.2), 50.3 cc (SD, ± 32.6), and 26.9 cc (SD, ± 18.6), respectively. All of the local failures occurred within the high-dose region. All of the locoregional failures occurred in patients who were treated with MRI guidance.

Twenty-nine patients (38%) experienced grade ≥ 2 acute toxicities, including diarrhea, nausea, cystitis, and proctitis. Five patients experienced acute grade 3 toxicity, including 2 with intractable nausea and vomiting and 3 with neutropenic fever. There were no grade ≥ 4 toxicities. The 2-year cumulative incidences of grade 1, 2, and 3 late toxicity were 31.8% (95% CI, 13.9%-49.6%), 10.8% (95%, 3.1%-24.1%), and 2.2% (0.17%-10.1%), respectively. One patient experienced late grade 3 GI toxicity. She presented 7 months after completion of brachytherapy with hematochezia. She underwent colonoscopy, which revealed a benign sigmoid stricture at 20 cm with telangiectasias, which required laser coagulation. No other late grade ≥ 3 toxicity was observed.

Discussion

The use of image guided EBRT has become increasingly prevalent in recent years ([27](#)), whereas the practice of brachytherapy is still largely dependent on point-based treatment techniques that do not account for anatomic variations in tumors and normal tissues. Although several reports from the GEC-ESTRO working group ([17-20](#)) support MRI-based IGBT, little evidence has been available for CT-based planning. This is one of the largest reports to date on clinical outcomes in patients treated with CT-based IGBT. We found that CT-based IGBT provides excellent local control, with relatively low rates of acute and late toxicity.

In comparison with previously published reports of IGBT ([Table 4](#)), the rates of tumor control and toxicity achieved with CT-based IGBT in this report appear similar. This study demonstrated a local failure rate of only 5.8%, which is remarkable, considering that two-thirds of patients had at least stage IIB disease. It should be noted that the majority of patients in this report were treated with IMRT, which may at least partially explain the rates of low toxicity compared with historical controls. Nonetheless, the rate of

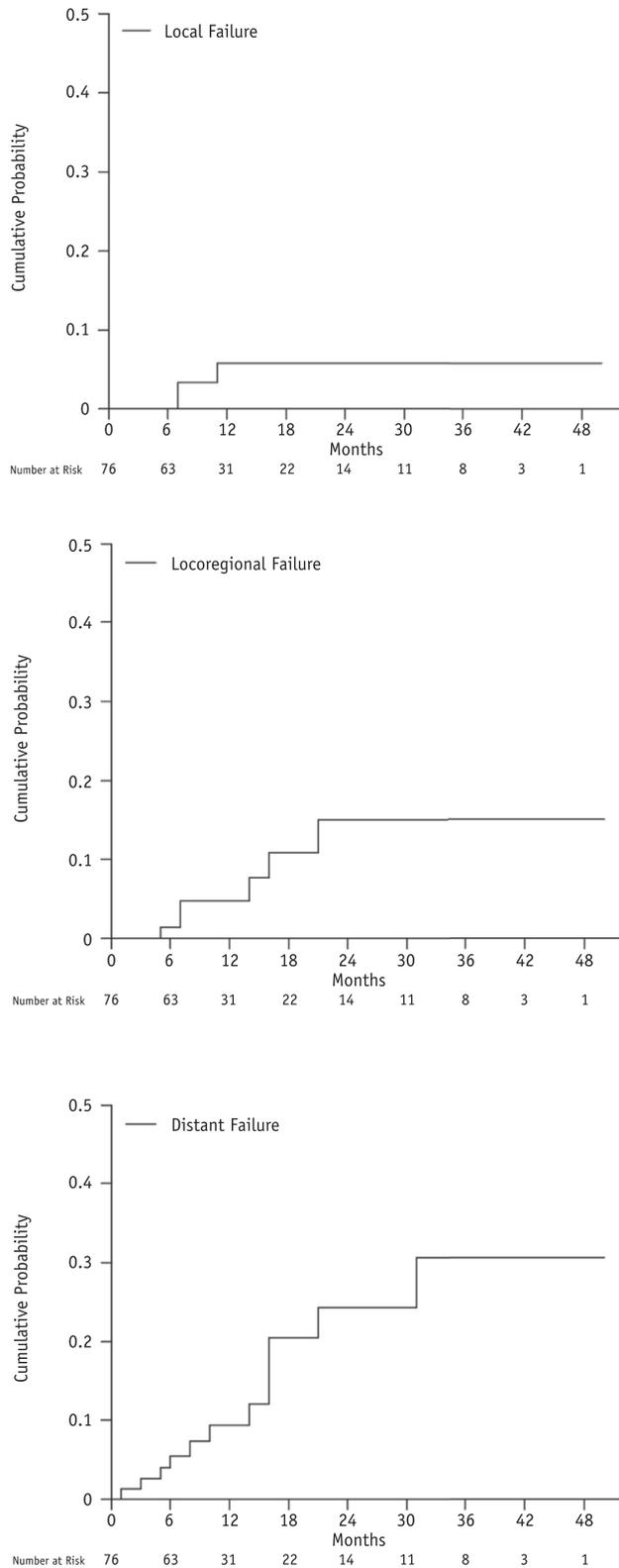


Fig. 2. Cumulative incidence of local (above), locoregional (middle), and distant failure (below).

severe toxicity was low, with only 5 cases of acute grade 3 toxicity. One patient experienced grade 3 GI toxicity. A review of her plan demonstrated a loop of sigmoid colon within 2 cm of the tandem (Fig. 4). The sigmoid D2cc from

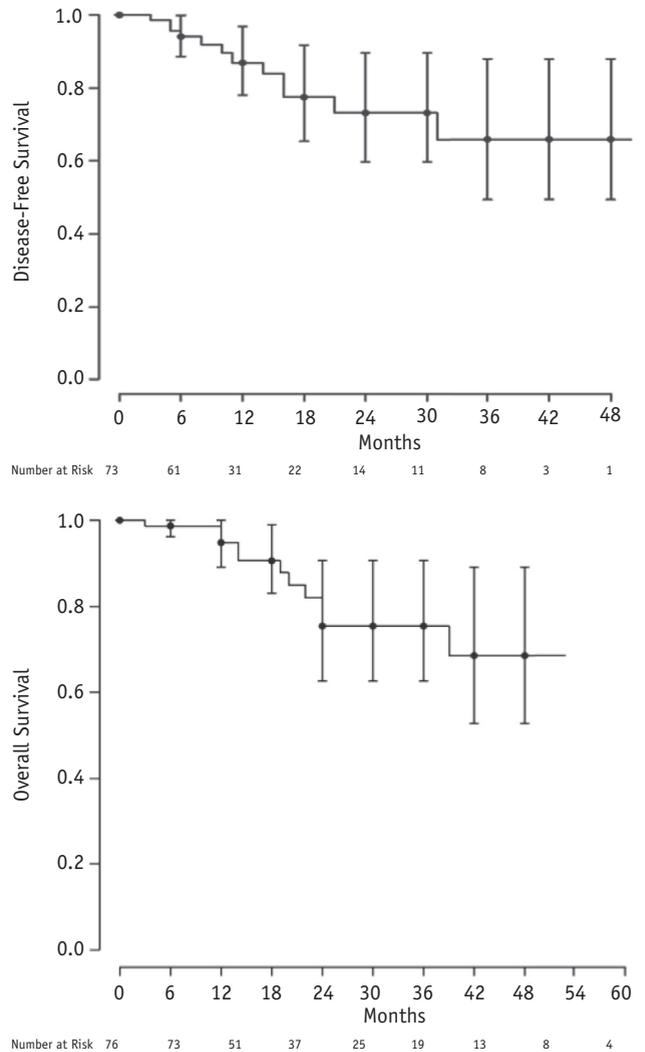


Fig. 3. Disease-free (above) and overall (below) survival. The error bars demonstrate the 95% confidence intervals.

her plan was 75 Gy. This is notable, considering that this dose would have been much higher, if the prescription dose had been delivered to points A. No other cases of severe late toxicity have been observed to date. However, these results should be interpreted with caution because of our limited follow-up time.

This CT-based planning also offers a distinct advantage over MRI-based planning. Owing to cost and access issues, obtaining an MRI at every implantation may not be feasible in most practices. Conversely, the vast majority of practices in the developed world have ready access to CT simulation. Thus, CT-based planning with MRI guidance offers a desirable alternative for practices with limited or no access to MRI. There is evidence that compared with MRI-based planning, CT-based planning results in different shapes and sizes of the HRCTV and OARs (28, 29), but these differences are small and do not result in different dose parameters when volume optimization is used (28, 30). The results from this report suggest that these discrepancies between MRI-based and CT-based planning may not be clinically significant.

Table 4 Comparison of clinical outcomes between studies of image guided brachytherapy for cervical cancer

Study	Patients (n)	Follow-up time (y)	LC (%)	DFS (%)	OS (%)	Severe late toxicity* (%)			
						Bladder	Rectal	Bowel	Vaginal
Potter et al (19)	156	3	95	75	68	2	5	0	1
Beriwal et al (22)	44	2	88	85	86	0	0	0	0
Present series	76	2	94	70	75	1.5	0	0	0

Abbreviations: DFS = disease-free survival; LC = local control; OS = overall survival.

* Defined as grade ≥ 3 occurring 90 days after the start of treatment.

However, MRI does provide better soft tissue delineation, especially for distinguishing the uterine adnexa from surrounding tissues, so at least 1 MRI is helpful. Furthermore, a recent study found that CT-based planning with an MRI done only at the first fraction provided similar target coverage and normal tissue sparing compared with fully MRI-based planning, particularly in low-volume disease (23). It should be noted that nearly 25% of the patients in this report were treated without MRI guidance, with no apparent clinical detriment. Thus, it is possible that solely CT-based planning may provide similar outcomes, but larger groups of patients with longer follow-up times are necessary to draw such conclusions. We emphasize that these results are preliminary and that this technique should be evaluated further in a prospective setting before becoming widely used in a community setting.

There are some notable limitations to this study. The largest limitation is the relatively short follow-up time compared with those of older studies. This is particularly important in terms of late toxicity, which requires several years of follow-up for adequate assessment. Nonetheless, the early toxicity results presented herein are excellent. Additionally, this study is subject to the biases inherent in retrospective studies, which may underestimate the rates of

toxicity and disease recurrence as a result of poor data collection. However, since adopting this technique we have been meticulous in recording our dosimetric information and clinical events to ensure high-quality data.

This report adds to the growing body of evidence supporting the effectiveness and safety of IGBT for the treatment of cervical cancer. Further research is needed to evaluate long-term outcomes and better define the clinical and dosimetric predictors of toxicity and tumor control. IGBT is now the subject of the prospective, multi-institutional EMBRACE study (www.embracestudy.dk), which was initiated by GEC-ESTRO investigators. However, to our knowledge there are currently no such ongoing studies in the United States. We hope to implement our CT-based technique as part of future prospective studies, and we hope this report encourages other centers to become involved in similar endeavors.

References

1. Tod M, Meredith WJ. Treatment of cancer of the cervix uteri: A revised Manchester method. *Br J Radiol* 1953;26:252-257.
2. Tod M, Meredith WJ. A dosage system for use in the treatment of cancer of the uterine cervix. *Br J Radiol* 1938;11:809-824.
3. Sun LM, Huang EY, Ko SF, et al. Computer tomography-assisted three-dimensional technique to assess rectal and bladder wall dose in intracavitary brachytherapy for uterine cervical cancer. *Radiation Oncol* 2004;71:333-337.
4. Potter R, Dimopoulos J, Georg P, et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiation Oncol* 2007;83:148-155.
5. Datta NR, Srivastava A, Maria Das KJ, et al. Comparative assessment of doses to tumor, rectum, and bladder as evaluated by orthogonal radiographs vs. computer enhanced computed tomography-based intracavitary brachytherapy in cervical cancer. *Brachytherapy* 2006;5:223-229.
6. Koom WS, Sohn DK, Kim JY, et al. Computed tomography-based high-dose-rate intracavitary brachytherapy for uterine cervical cancer: Preliminary demonstration of correlation between dose-volume parameters and rectal mucosal changes observed by flexible sigmoidoscopy. *Int J Radiat Oncol Biol Phys* 2007;68:1446-1454.
7. Barillot I, Horiot JC, Maingon P, et al. Maximum and mean bladder dose defined from ultrasonography: Comparison with the ICRU reference in gynaecological brachytherapy. *Radiation Oncol* 1994;30:231-238.
8. Schoepel SL, LaVigne ML, Martel MK, et al. Three-dimensional treatment planning of intracavitary gynecologic implants: Analysis of ten cases and implications for dose specification. *Int J Radiat Oncol Biol Phys* 1994;28:277-283.
9. Ling CC, Schell MC, Working KR, et al. CT-assisted assessment of bladder and rectum dose in gynecological implants. *Int J Radiat Oncol Biol Phys* 1987;13:1577-1582.

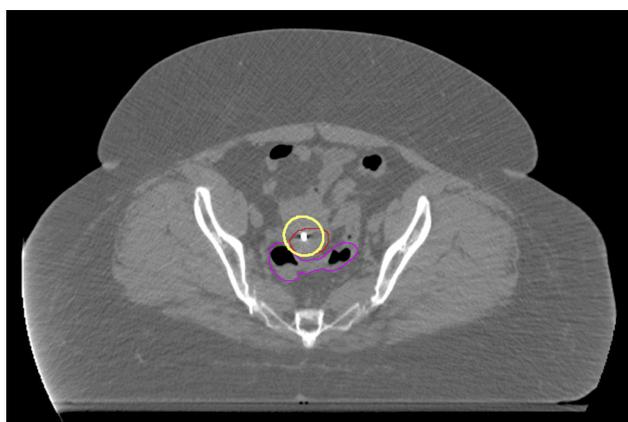


Fig. 4. Axial computed tomography slice used for brachytherapy planning in a patient who experienced a sigmoidal stricture with telangiectasias 7 months after treatment. The contours demonstrate the high-risk clinical target volume (red), the 100% isodose line (yellow), and the sigmoid colon (magenta). A color version of this figure is available at www.redjournal.org.

10. van den Bergh F, Meertens H, Moonen L, et al. The use of a transverse CT image for the estimation of the dose given to the rectum in intracavitary brachytherapy for carcinoma of the cervix. *Radiother Oncol* 1998;47:85-90.
11. Mazeron R, Kamsu Kom L, Rivin Del Campo E, et al. Comparison between the ICRU rectal point and modern volumetric parameters in brachytherapy for locally advanced cervical cancer. *Cancer Radiother* 2014;18:177-182.
12. Georg P, Potter R, Georg D, et al. Dose effect relationship for late side effects of the rectum and urinary bladder in magnetic resonance image-guided adaptive cervix cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2012;82:653-657.
13. Perez CA, Grigsby PW, Lockett MA, et al. Radiation therapy morbidity in carcinoma of the uterine cervix: Dosimetric and clinical correlation. *Int J Radiat Oncol Biol Phys* 1999;44:855-866.
14. Roeske JC, Mundt AJ, Halpern H, et al. Late rectal sequelae following definitive radiation therapy for carcinoma of the uterine cervix: A dosimetric analysis. *Int J Radiat Oncol Biol Phys* 1997;37:351-358.
15. Kottmeier HL, Gray MJ. Rectal and bladder injuries in relation to radiation dosage in carcinoma of the cervix: A 5-year follow-up. *Am J Obstet Gynecol* 1961;82:74-82.
16. Perez CA, Fox S, Lockett MA, et al. Impact of dose in outcome of irradiation alone in carcinoma of the uterine cervix: Analysis of two different methods. *Int J Radiat Oncol Biol Phys* 1991;21:885-898.
17. Haie-Meder C, Potter R, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC-ESTRO working group (i): Concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol* 2005;74:235-245.
18. Potter R, Haie-Meder C, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006;78:67-77.
19. Potter R, Georg P, Dimopoulos JC, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol* 2011; 100:116-123.
20. Dimopoulos JC, Lang S, Kirisits C, et al. Dose-volume histogram parameters and local tumor control in magnetic resonance image-guided cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2009;75: 56-63.
21. Georg P, Lang S, Dimopoulos JC, et al. Dose-volume histogram parameters and late side effects in magnetic resonance image-guided adaptive cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2011;79:356-362.
22. Beriwal S, Kannan N, Kim H, et al. Three-dimensional high dose rate intracavitary image-guided brachytherapy for the treatment of cervical cancer using a hybrid magnetic resonance imaging/computed tomography approach: Feasibility and early results. *Clin Oncol (R Coll Radiol)* 2011;23:685-690.
23. Nesvacil N, Potter R, Sturdza A, et al. Adaptive image guided brachytherapy for cervical cancer: A combined MRI-/CT-planning technique with MRI only at first fraction. *Radiother Oncol* 2013;107:75-81.
24. Simpson DR, Yashar CM, Kannan N, et al. CT and MRI-based image guided brachytherapy for cervical cancer: A multi-institutional report. *Int J Radiat Oncol Biol Phys* 2012;84:S19.
25. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-481.
26. Dignam JJ, Kocherginsky MN. Choice and interpretation of statistical tests used when competing risks are present. *J Clin Oncol* 2008;26: 4027-4034.
27. Simpson DR, Lawson JD, Nath SK, et al. A survey of image-guided radiation therapy use in the United States. *Cancer* 2010;116:3953-3960.
28. Eskander RN, Scanderbeg D, Saenz CC, et al. Comparison of computed tomography and magnetic resonance imaging in cervical cancer brachytherapy target and normal tissue contouring. *Int J Gynecol Cancer* 2010;20:47-53.
29. Viswanathan AN, Dimopoulos J, Kirisits C, et al. Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: Results of a prospective trial and preliminary guidelines for standardized contours. *Int J Radiat Oncol Biol Phys* 2007;68:491-498.
30. Wang B, Kwon A, Zhu Y, et al. Image-guided intracavitary high-dose-rate brachytherapy for cervix cancer: A single institutional experience with three-dimensional CT-based planning. *Brachytherapy* 2009;8: 240-247.