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Intensity Modulated Radiation Therapy and Image-Guided Adapted Brachytherapy for Cervix Cancer

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Summary

Intensity modulated radiation therapy and 3-dimensional image-guided adapted brachytherapy are increasingly used for definitive cervical cancer treatment. We compared patterns of failure and survival in patients treated with these modalities with results from patients treated with 2-dimensional external beam radiation therapy and brachytherapy. All patients received a pretreatment positron emission tomography scan, and all surviving patients had a minimum of 5 years of follow-up. Intensity modulated radiation therapy and 3-dimensional image-guided adapted brachytherapy were associated with higher survival and reduced late bowel and bladder toxicities compared with 2-dimensional external beam radiation therapy and brachytherapy.

Purpose—This study reported long-term outcomes of patients with cervical cancer who were treated with intensity modulated radiation therapy and 3-dimensional (3D) image-guided adapted brachytherapy (IMRT/3D-IGABT) compared with those treated with 2-dimensional (2D) external irradiation and 2D brachytherapy (2D EBRT/BT).

Methods and Materials—This study included patients with newly diagnosed cervical cancer and pretreatment fluorodeoxyglucose positron emission tomography scans who were treated with curative-intent irradiation from 1997 to 2013. The treatment policy changed from using 2D EBRT/BT to IMRT/3D-IGABT in 2005. Patterns of recurrence, cancer-specific survival (CSS), and overall survival (OS) were evaluated. Late gastrointestinal and genitourinary toxicity were scored with National Cancer Institute Common Terminology Criteria for Adverse Events.

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Results—The median follow-up for patients alive at the time of last follow-up in the 2D EBRT/BT group ($n = 300$) was 15.3 years (range, 10.8–20.5 years). In the IMRT/3D-IGABT group ($n = 300$), it was 7 years (range, 5–12.4 years). According to the International Federation of Gynecology and Obstetrics, 33% of tumors were stage IB1 to IB2, 41% were stage IIA to IIB, and 26% were stage IIIA to IVA. The results after 5 years for patients treated with 2D EBRT/BT showed that freedom from relapse (FFR) was 57%, CSS was 62%, and OS was 57%. For the IMRT/3D-IGABT group, the 5-year results showed that FFR was 65% ($P = .04$), CSS was 69% ($P = .01$), and OS was 61% ($P = .04$). When stratified by lymph node status according to positron emission tomography scan results, disease control was most improved with IMRT/3D-IGABT versus 2D EBRT/BT in patients with positive pelvic lymph nodes only ($P = .02$). Cumulatively, 88 of 600 patients (15%) had grade 3 late bowel/bladder toxicity. The 2D EBRT/BT group had 55 patients (18%), and the IMRT/3D-IGABT group had 33 patients (11%; $P = .02$).

Conclusions—IMRT/3D-IGABT was associated with improved survival and decreased gastrointestinal and genitourinary toxicity in patients with cervical cancer compared with those who received 2D EBRT/BT.

Introduction

Chemoradiation is the standard treatment for locally advanced cervical cancer.¹ The method of delivering radiation has evolved with technical improvements in imaging and treatment delivery. Compared with 2-dimensional (2D) or 3-dimensional (3D) external beam radiation therapy (EBRT), intensity modulated radiation therapy (IMRT) uses multiple beam angles and field shapes to deliver doses to the clinical target while sparing normal organs, such as the bowel, rectum, bladder, and marrow-containing pelvic bones.^{2–10} Similarly, 3D image-guided adapted brachytherapy (3D-IGABT) with computed tomography (CT) or magnetic resonance imaging (MRI) has been increasingly used to improve target coverage and decrease the dose to organs at risk.¹¹ Reported long-term outcomes for patients with intact cervical cancer treated with both IMRT and 3D-IGABT are lacking.

Our institution began treating locally advanced cervical cancer with both IMRT and 3D-IGABT in 2005, transitioning from 2D brachytherapy to CT-guided brachytherapy in 2005 and then to MRI-guided brachytherapy in 2007. Fluorodeoxyglucose positron emission tomography (FDG-PET) scans have also been used at our institution in all patients with cervical cancer since 1997 to evaluate the primary tumor, lymph nodes, and distant sites of metastatic disease, and to direct therapy to the primary tumor and involved nodes.¹² Previously, we treated the pelvis with opposed anteroposteriore–posteroanterior radiation fields and a midline step-wedge block.

The IMRT technique was developed to emulate the midline step-wedge dose distribution with a further dose reduction to normal pelvic tissues from external irradiation, which maximizes the dose delivered to the tumor with brachytherapy.¹³ Brachytherapy starts concurrently with the external treatment. Early results of this method suggested excellent local control and cancer-specific survival (CSS) with limited toxicity.^{8,14,15} This updated study reports the long-term clinical outcomes of patients with a minimum follow-up of 5 years.

Methods and Materials

Patients

This study included 600 consecutive patients with newly diagnosed cervical cancer and pretreatment FDG-PET scans who were treated with curative-intent radiation from June 1997 to June 2013. The current study includes all patients reported in our initial publication.⁸ Patient follow-up was updated for patients included in the initial published analysis,⁸ and 148 patients were added. All patients underwent a pretreatment staging workup, including a history and physical examination; examination under anesthesia; cervical tumor biopsy; pelvic CT or MRI scans; and whole-body FDG-PET, PET/CT, or PET/MRI scans. Patients were not surgically staged. Patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) clinical staging criteria (irrespective of their FDG-PET lymph node status). Patients with clinically occult FDG-avid supraclavicular nodes (all biopsy proven) were included but assigned to their FIGO clinical stage. Patients with FIGO IVB stage disease or who received brachytherapy alone were excluded. This retrospective analysis was approved by our institutional review board with waiver of informed consent (institutional review board number 201807142).

External radiation treatment

From 1997 to 2005, 300 patients were treated with a combination of whole-pelvis and split-field irradiation using our institutional step-wedge technique.¹⁶ Afterward, an additional 300 patients were treated with PET-guided IMRT designed to replicate the step-wedge technique plans, with the pelvic lymph nodes receiving the full external dose (50.4 Gy) and the cervical tumor receiving approximately 20 Gy from the external irradiation. Metabolically active nodes were not prescribed additional boost irradiation in either group. Details of simulation and treatment planning were previously described.^{8,14} The metabolic tumor volume was contoured at the 40% threshold and prescribed 20 Gy. The pelvic vessels were contoured from the bifurcation of the aorta to the medial circumflex arteries and included the internal iliac and obturator nodes.

Paraortic vessels were contoured up to the renal vessels only if paraortic nodes were metabolically involved. In addition to metabolically active lymph nodes, the clinical treatment volume was a 7-mm expansion of the vessels contour excluding pelvic bones and vertebrae. In 2007, we transitioned from daily orthogonal kilovoltage imaging to daily megavoltage cone beam CT before treatment to account for setup uncertainties.¹⁷ A planning treatment volume (PTV) expansion of 5 to 7 mm was prescribed to 50.4 Gy. Patients with biopsy-proven supraclavicular nodes were not treated with neck irradiation in this cohort.

Intracavitary brachytherapy

Nearly all patients who did not have IMRT (99.7%) were treated with 2D brachytherapy, and 92% of patients treated with IMRT had 3D-IGABT ($P < .001$). Therefore, the comparison groups were defined as 2D external beam radiation therapy/2D brachytherapy (2D EBRT/BT) and IMRT/3D-IGABT for this study. In the 2D EBRT/BT group, approximately 60% of patients were treated with high-dose-rate (HDR) brachytherapy delivered in 6

weekly fractions of approximately 6.5 Gy per fraction to point A using a ^{192}Ir source and tandem and ovoid intracavitary applicators. The rest (40%) had low-doserate (LDR) brachytherapy with two Cesium-137 intracavitary Fletcher-Suit-Delclos implants. All patients in the IMRT/3D-IGABT group received HDR brachytherapy. Beginning on week 1 of external irradiation, patients received 4 weekly fractions of external irradiation and 1 weekly HDR fraction.

In March 2005, our institution made the change from 2D point A planning to CT IGABT. Starting in July 2007, MRI IGABT was instituted and treatment planning parameters were previously described.^{14,15} Briefly, the treating physician delineated the tumor based on the T2-weighted and apparent diffusion coefficient MRI images. The dosimetrist would then contour the bladder, rectum, and sigmoid colon on the T2-weighted images. The ^{192}Ir source dwell position and times were then adapted weekly to replicate the classic “pear-shaped” dose distribution to maximize dose to the tumor and minimize dose to normal structures.

Chemotherapy

Concurrent cisplatin was received by 89% of patients (85% of patients in the 2D EBRT/BT group and 92% of patients in the IMRT/3D-IGABT group, $P = .007$). Of these patients, 94% (97% in the 2D EBRT/BT group and 94% in the IMRT/3D-IGABT group, $P = .35$) received at least 4 cycles of chemotherapy.

Outcomes

Patients were followed with clinical examinations approximately every 2 months for the first 6 months, every 3 months for the next 2 years, and then every 6 months. FDG-PET was performed 3 months after completion of treatment in most patients and then as indicated by clinical examination or symptoms. The sites and timing of any recurrence or toxicity were recorded. Survival, tumor recurrence, and complications were measured from the date of each patient's initial diagnostic PET scan. Locoregional failure (LRF) was defined as any failure in the PTV and distant failure (DF) as failure beyond the PTV (including paraortic failures where the PTV only included the pelvis). Patterns of failure were only recorded at time of first recurrence, and events for LRF and DF were both censored if they were found simultaneously. Regional control (RC), distant control (DC), freedom from relapse (FFR), CSS, and overall survival (OS) were censored for LRF, DF, any recurrence, death from cervical cancer, and death from any cause, respectively. National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 was used to score the maximum late toxicity. Outcomes were also censored on the date of the last clinical follow-up.

Statistical analyses

For baseline comparisons, the Fisher exact test was used to compare categorical data, and the nonparametric Mann-Whitney U test was used for continuous variables. The Kaplan-Meier (product-limit) method was used to derive estimates of survival based on total sample size. The test of equivalence of survival was performed by the generalized Wilcoxon (log-rank) test. The cumulative hazard function was used to compare the rates at conditional times for the development of grades 3 and greater bowel and bladder complications. Cox regression analysis was performed for both univariable and multivariable modeling of CSS.

Factors significant on univariable analysis ($P < .1$) were entered in a forward-conditional multivariable model. Final significance was defined as $P < .05$, and all tests were 2-tailed. Statistical analyses were done in SPSS, version 23 (IBM, Armonk, NY).

Results

Patient characteristics

The patient and treatment characteristics of the 2D EBRT/BT and IMRT/3D-IGABT groups are shown in Table 1. Most tumors were squamous cell histology (86%), and most were FIGO stage II or higher (67%). Compared with the 2D EBRT/BT group, patients treated with IMRT/3D-IGABT had a lower frequency of only pelvic nodal involvement by PET but a higher frequency of both pelvic and paraortic nodal involvement ($P = .03$). Twelve patients (4%) had clinically occult but FDG-avid supraclavicular nodes (all biopsy-proven positive). They were treated with curative-intent pelvic and paraortic irradiation and did not receive irradiation to the clinically occult FDG-positive supraclavicular lymph nodes.

Recurrence and survival in patients treated with IMRT/3D-IGABT versus 2D EBRT/BT

The median follow-up for all patients alive at the time of last follow-up was 10.6 years, with a range of 5 to 19.7 years. The median follow-up was 15.3 years for the 2D EBRT/BT group (range, 10.8–19.7 years) and 7.2 years for the IMRT/3D-IGABT group (range, 5–12.4 years). At the time of last follow-up, there were 249 recurrences (42%), 225 deaths from cervical cancer (38%), and 309 deaths from any cause (52%). Figure 1 shows no difference between the 2D EBRT/BT and IMRT/3D-IGABT groups for RC, but DC, FFR, CSS, and OS were all significantly higher in patients receiving IMRT/3D-IGABT compared with those who had 2D EBRT/BT. For patients receiving 2D EBRT/BT, the 5- and 10-year results, respectively, were 78% and 75% for RC, 65% and 60% for DC, 57% and 51% for FFR, 62% and 54% for CSS, and 57% and 44% for OS. For patients receiving IMRT/3D-IGABT, the corresponding 5- and 10-year outcomes, respectively, were 81% and 79% for RC ($P = .50$), 72% and 70% for DC ($P = .03$), 65% and 62% for FFR ($P = .04$), 69% and 68% for CSS ($P = .01$), and 61% and 57% for OS ($P = .04$). On univariable Cox regression, higher FIGO stage, larger tumor volume, and FDG-avid lymph nodes were associated with worse CSS ($P < .05$); IMRT/3D-IGABT was associated with higher CSS ($P < .05$). Chemotherapy, histology, age, and HDR (vs LDR) brachytherapy were not associated with CSS ($P > .05$). The final multivariable model included FIGO stage, PET lymph node status, and IMRT/3D-IGABT versus 2D EBRT/BT (Table 2).

Recurrence and survival in patients treated with IMRT/3D-IGABT versus 2D EBRT/BT, stratified by PET lymph node status

Because PET lymph node status was a strong predictor of outcomes independent of other clinical and treatment variables, we evaluated whether IMRT was associated with FFR and CSS in patients with no positive lymph nodes; positive pelvic nodes alone; positive pelvic and paraortic nodes; and positive pelvic, paraortic, and supraclavicular nodes. When stratified by PET lymph node status, FFR was significantly improved with IMRT/3D-IGABT versus 2D EBRT/BT in patients with positive pelvic lymph nodes ($P = .02$, Fig. 2B). No difference in FFR was found for patients with negative lymph nodes or in patients with

positive pelvic and paraortic nodes ($P > .05$, Figs. 2 A and C). IMRT/3D-IGABT improved CSS in patients without FDG-avid lymph nodes ($P = .055$, Fig. 2D) and did not have an effect on patients with positive pelvic or pelvic and paraortic lymph nodes (Figs. 2 E–F).

Recurrence and survival in patients treated with IMRT/3D-IGABT versus 2D EBRT/BT in the chemoradiation subgroup

A sensitivity analysis of only patients receiving chemoradiation showed similar results compared with the whole cohort (Fig. E1; available online at <https://doi.org/10.1016/j.ijrobp.2018.11.012>). The patients receiving 2D EBRT/BT had 5- and 10-year rates of 79% and 77% for RC, 63% and 59% for DC, 62% and 55% for CSS, and 56% and 46% for OS, respectively. The patients receiving IMRT/3D-IGABT had corresponding 5- and 10-year rates of 81% and 80% for RC ($P = .61$), 72% and 70% for DC ($P = .02$), 70% and 68% for CSS ($P = .001$), and 63% and 62% for OS ($P = .006$; Fig. E1; available online at <https://doi.org/10.1016/j.ijrobp.2018.11.012>).

Late toxicities in patients treated with IMRT/3D-IGABT versus 2D EBRT/BT

In 88 of the 600 patients (14.7%), grade 3 late bowel or bladder toxicities were found. In the 2D EBRT/BT group, 55 of 300 patients (18.3%) had these toxicities versus 33 of 300 patients (11%) in the IMRT/3D-IGABT group ($P = .01$). Table 3 summarizes the late gastrointestinal and genitourinary toxicities experienced in each group. Figure 3 shows the estimated 5- rates of either late bowel or bladder grade 3 toxicity for the 2D EBRT/BT and IMRT/3D-IGABT groups (21% vs. 11%, respectively; log-rank, $P = .02$). Of the 24 patients with rectovaginal fistula, 4 fistulas (17%) developed in patients with a local tumor recurrence (3 in the 2D EBRT/BT group vs 1 in the IMRT/3D-IGABT group). Of the 19 patients with vesicovaginal fistula, 6 fistulas (32%) developed in patients with a local tumor recurrence (5 in the 2D EBRT/BT group vs 1 in the IMRT/3D-IGABT group).

Discussion

In 2010, we reported our initial experience showing late toxicities were significantly less frequent with IMRT/3D-IGABT compared with 2D EBRT/BT. Survival was statistically greater with IMRT/3D-IGABT, although follow-up was limited.⁸ This analysis with a 5-year minimum follow-up confirms our initial toxicity findings, and it also shows that disease relapse and survival curves begin to diverge after about 3 years with an IMRT/3D-IGABT advantage sustained out to 10 years. Improved disease control and survival are likely secondary to more accurate radiation delivery, although in our cohort we cannot separate out the effects of IMRT from those of 3D-IGABT because both were implemented at approximately the same time. PET-guided planning to visualize and target the tumor and FDG-avid lymph nodes may have allowed for improved coverage of pelvic lymph nodes with IMRT compared with 2D EBRT, especially in patients with positive pelvic lymph nodes. IMRT may also decrease the frequency of radiation-induced lymphopenia by reducing dose to the bone marrow. This study is the first large study with prolonged follow-up showing that IMRT/3D-IGABT improves survival over 2D techniques. This study is important to benchmark how improvements in radiation delivery have affected clinical outcomes.

A study from Taiwan also compared IMRT and 3D-IGABT for PET-staged cervical cancer to historical controls treated with 2D EBRT and brachytherapy.¹⁸ In that study, 72 patients were treated with extended-field pelvic and paraortic 3D radiation to 41.4 to 45 Gy, followed by an IMRT boost to 54 Gy to the same region. FDG-avid pelvic and paraortic nodes were then sequentially boosted up to 59.4 to 64.8 Gy. In results that were similar to those of our cohort, 90% of patients received at least 4 cycles of concurrent chemotherapy. Disease-free survival (DFS) at 5 years for patients with pelvic alone and pelvic + paraortic positive lymph nodes was 78.5% and 41.8%, respectively. Compared with FIGO stage-matched historical controls, the 8-year OS improved from 41.2% to 70.1% ($P = .0015$). However, the historical controls did not have pretreatment PET imaging, so it is unclear whether the benefit was from patients with less nodal disease, from IMRT technique, or from more aggressive nodal boost doses. All our patients received pretreatment PET and were prescribed a standard external radiation dose without additional boosts to FDG-avid nodes. The 5-year FFR for our patients with pelvic alone and pelvic + paraortic positive lymph nodes was 71% and 30%, respectively, which compares favorably to the Taiwanese results. The efficacy of boosting FDG-avid nodes remains an open question, although IMRT boosts at least appear to limit late toxicity.^{18,19}

Other single-institution reports on IMRT with 2D brachytherapy for treatment of locally advanced cervical cancer may allow some comparison with our IMRT/3D-IGABT results. Hasselle et al compiled data from 111 patients with cervical cancer from 3 institutions. Their 3-year DFS, OS, and late grade 3 toxicity were 69%, 78%, and 7%, respectively.⁷ Chen et al reported on 109 patients with cervical cancer from Taiwan; their 3-year DFS, OS, and late grade 3 toxicity were 68%, 78%, and 11%, respectively.⁶ A recent study from China limited to 373 patients with cervical cancer in FIGO stage IIB who were treated with IMRT and 2D brachytherapy found 3-year DFS, OS, and late grade 3 toxicity to be 82.2%, 87.5%, and 5.1%, respectively.²⁰ Our IMRT/3D-IGABT cohort had 3-year FFR and OS of 67% and 70%, respectively. DFS and FFR appear similar across these reports, suggesting that 3D-IGABT may only incrementally change overall disease control compared with 2D brachytherapy.

The patients who benefited the most from IMRT/3D-IGABT in our study had FDG-avid pelvic nodes only. When treating with a split-field pelvis, most of the radiation dose to the primary tumor comes from brachytherapy, and we did not see a difference in locoregional control with IMRT/3D-IGABT versus 2D EBRT/BT. A potential criticism of using IMRT to treat cervical cancer has been marginal misses because of tumor motion from week to week.²¹ We did not experience this problem because most of the dose to the cervix was delivered with brachytherapy, which moves with the tumor. However, patients were more likely to develop distant metastasis if they had FDG-avid pelvic nodes and were treated with 2D EBRT/BT. It is possible that some patients in the 2D EBRT/BT group had subclinical paraortic nodes that were not detected by FDG-PET (without CT), leading to worse outcomes in the 2D EBRT/BT group compared with the IMRT/3D-IGABT group, in which all patients received a PET/CT scan. Before we implemented IMRT, CT and PET/CT simulation were also not part of our planning process for the external irradiation. It is possible that the pelvic lymph nodes were not completely covered and therefore received an underdose of 2D external radiation.²²

Patients with FDG-avid pelvic + paraortic and pelvic + paraortic + supraclavicular nodes did poorly. For patients with FDG-avid pelvic and paraortic nodes, IMRT/3D-IGABT did not change recurrence patterns or survival outcomes compared with patients receiving 2D EBRT/BT. The Gynecologic Oncology Group studies in the 1980s, which included a mix of postoperative radiation and definitive radiation, dosed the paraortic lymph nodes to 44 to 60 Gy and achieved a 3-year survival of about 25%.²³ In the 1990s, adding concurrent 5-fluorouracil and cisplatin to 2D extended-field radiation therapy resulted in a 3-year progression-free survival of 33%.²⁴ The RTOG 9210 study designed a hyperfractionated (1.2 Gy twice daily) radiation regimen with a sequential paraortic boost up to 58 Gy delivered with concurrent 5-fluorouracil and cisplatin. The 3-year freedom-from-disease relapse rate was 37%, and late grade 4 toxicity was unacceptably high (17%).²⁵ In our current study using IMRT/3D-IGABT, standard fractionation irradiation, and concurrent cisplatin, the 3-year freedom-from-disease relapse rate was 35%. We hypothesize that patients with positive pelvic and paraortic lymph nodes at diagnosis have undetectable micrometastatic spread of their disease at diagnosis that is not controlled with concurrent systemic therapy and that irradiation technique has no marginal benefit. New systemic therapies will need to be explored to improve outcomes in this subset of patients.²⁶

Limiting toxicity is a goal of IMRT/3D-IGABT. Late grade 3 toxicity was reduced for all patients, including patients with paraortic nodal disease treated with IMRT/3D-IGABT. In other series irradiating paraortic nodes with IMRT, the rate of late grade 3 toxicity was 5% to 10%.^{5,18,27,28} Prospectively assessed multi-institutional data are now available from the EMBRACE study reporting on acute and late toxicities after 3D or IMRT external radiation with MRI IGABT for locally advanced cervical cancer. With this study including more than 1000 patients, a third of whom had IMRT, the reported late grade 3 toxicity for bowel, bladder, lower leg edema, and hot flashes was 5.9%, 5.3%, 0.5%, and 1.9%, respectively.^{29–32} The recurrence and survival outcomes of EMBRACE are maturing, but results are promising enough that EMBRACE II has been opened to evaluate outcomes prospectively after IMRT and MRI-IGABT.¹¹ Our results presented here are comparable to those from the GEC-ESTRO approach.

Cervical cancer IMRT has also been shown prospectively to reduce bone marrow toxicity. The INTERTECC 2 phase 2 trial reported that for patients treated with specific dose constraints on the pelvic and vertebral bone marrow, there was a significant reduction in grade 3 neutropenia (8.6% vs 27.1%, $P = .04$) and a nonsignificant lower incidence of leukopenia (31.4% vs 43.8%, $P = .25$).³³ Retrospective data have shown that treatment-induced lymphopenia^{34,35} and neutrophil nadir³⁶ have been associated with poor survival in cervical cancer. This outcome could be because of poor chemotherapy tolerance or repression of immune cell surveillance. In our cohort, there was no difference in the number of patients who were able to tolerate at least 4 cycles of chemotherapy. INTERTECC 3 (NCT01554397) is a randomized phase 3 trial comparing standard IMRT to bone marrow-sparing IMRT with a primary objective of progression-free survival. The results may provide some rationale for improved systemic control with IMRT compared with 2D external irradiation.

The limitations of this retrospective analysis are that it compares patient outcomes in different cohorts over a long time span during which salvage chemotherapies have changed, possibly affecting survival after disease recurrence. Late toxicities may have been underreported because they were not assessed prospectively. Chemotherapy use was not balanced in the 2 groups, but results were similar in the subgroup of patients receiving chemoradiation. The IMRT/3D-IGABT had more nonsquamous histology tumors, but histology did not significantly correlate with CSS. We did subgroup analyses to correct for differences in the frequency of pelvic and paraortic lymph nodes between the IMRT/3D-IGABT and 2D EBRT/BT groups. Our institution switched from 2D planning to PET-CT simulation with IMRT and 3D-IGABT at about the same time, making it difficult to ascribe improvements in survival and toxicity to a single modality. These results are specific to how cervical cancer is treated at a single tertiary academic institution and cannot be generalized to all centers using IMRT/3D-IGABT. The strengths of this study are that it is the largest study of patients treated with PET/CT simulation, IMRT, and 3D-IGABT with a minimum of 5 years of follow-up. The results agree with other large series of patients treated with modern radiation and support the design of prospective trials that are currently accruing.

Conclusions

In the absence of randomized data comparing 2D EBRT/BT with IMRT/3D-IGABT techniques, this report suggests that the evolution of radiation delivery has improved survival while reducing toxicity for locally advanced cervical cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. National Comprehensive Cancer Network. Cervical cancer version 2.2018 Available at: https://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf Accessed December 28, 2018.
2. Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2002;52:1330–1337. [PubMed: 11955746]
3. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;56:1354–1360. [PubMed: 12873680]
4. Chen MF, Tseng CJ, Tseng CC, et al. Clinical outcome in post-hysterectomy cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy: Comparison

with conventional radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;67:1438–1444. [PubMed: 17394944]

5. Beriwal S, Gan GN, Heron DE, et al. Early clinical outcome with concurrent chemotherapy and extended-field, intensity-modulated radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2007; 68:166–171. [PubMed: 17321070]
6. Chen CC, Lin JC, Jan JS, et al. Definitive intensity-modulated radiation therapy with concurrent chemotherapy for patients with locally advanced cervical cancer. *Gynecol Oncol* 2011;122:9–13. [PubMed: 21514629]
7. Hasselle MD, Rose BS, Kochanski JD, et al. Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2011;80:1436–1445. [PubMed: 20708346]
8. Kidd EA, Siegel BA, Dehdashti F, et al. Clinical outcomes of definitive Intensity-modulated radiation therapy with fluorodeoxyglucose-positron emission tomography simulation in patients with locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys* 2010;77(4):1085–1091. [PubMed: 19880262]
9. Klopp AH, Moughan J, Portelance L, et al. Hematologic toxicity in RTOG 0418: A phase 2 study of postoperative IMRT for gynecologic cancer. *Int J Radiat Oncol Biol Phys* 2013;86:83–90. [PubMed: 23582248]
10. Liang Y, Bydder M, Yashar CM, et al. Prospective study of functional bone marrow-sparing intensity modulated radiation therapy with concurrent chemotherapy for pelvic malignancies. *Int J Radiat Oncol Biol Phys* 2013;85:406–414. [PubMed: 22687195]
11. Pötter R, Tanderup K, Kirisits C, et al. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018;9:48–60. [PubMed: 29594251]
12. Kidd EA, Siegel BA, Dehdashti F, et al. Lymph node staging by positron emission tomography in cervical cancer: Relationship to prognosis. *J Clin Oncol* 2010;28(12):2108–2113. [PubMed: 20308664]
13. Macdonald DM, Lin LL, Biehl K, et al. Combined intensity-modulated radiation therapy and brachytherapy in the treatment of cervical cancer. *Int J Radiat Oncol Biol Phys* 2008;71(2):618–624. [PubMed: 18407429]
14. Dyk P, Jiang N, Sun B, et al. Cervical gross tumor volume dose predicts local control using magnetic resonance Imaging/diffusion-weighted imaging guided high-dose-rate and positron emission tomography/computed tomography guided intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2014;90(4):794–801. [PubMed: 25245584]
15. Zoberi JE, Garcia-Ramirez J, Hu Y, et al. Clinical implementation of multisequence MRI-based adaptive intracavitary brachytherapy for cervix cancer. *J Appl Clin Med Phys* 2016;17(1):121–131. [PubMed: 26894342]
16. Perez CA, Kavanagh B. *Principle and Practice of Radiation Oncology: Uterine Cervix*. Vol 4th ed. Philadelphia: Lipincott, Williams & Williams; 2003.
17. Santanam L, Esthappan J, Mutic S, et al. Estimation of setup uncertainty using planar and MVCT imaging for gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2008;71(5):1511–1517. [PubMed: 18538499]
18. Chung YL, Horng CF, Lee PI, et al. Patterns of failure after use of ¹⁸F-FDG PET/CT in integration of extended-field chemo-IMRT and 3D-brachytherapy plannings for advanced cervical cancers with extensive lymph node metastases. *BMC Cancer* 2016;16:1–11.
19. Cihoric N, Tapia C, Krüger K, et al. IMRT with ¹⁸FDG-PET/CT based simultaneous integrated boost for treatment of nodal positive cervical cancer. *Radiat Oncol* 2014;9:1–8. [PubMed: 24382205]
20. Wang W, Meng Q, Hou X, et al. Efficacy and toxicity of image-guided intensity-modulated radiation therapy combined with dose-escalated brachytherapy for stage IIB cervical cancer. *Oncotarget* 2017;8: 102965–102973. [PubMed: 29262537]
21. Beadle BM, Jhingran A, Salehpour M, et al. Cervix regression and motion during the course of external beam chemoradiation for cervical cancer. *Int J Radiat Oncol Biol Phys* 2009;73:235–241. [PubMed: 18513882]

22. Finlay MH, Ackerman I, Tirona RG, et al. Use of CT simulation for treatment of cervical cancer to assess the adequacy of lymph node coverage of conventional pelvic fields based on bony landmarks. *Int J Radiat Oncol Biol Phys* 2006;64:205–209. [PubMed: 16198505]
23. Berman ML, Keys H, Creasman W, et al. Survival and patterns of recurrence in cervical cancer metastatic to periaortic lymph nodes (a Gynecologic Oncology Group study). *Gynecol Oncol* 1984;19:8–16. [PubMed: 6469092]
24. Varia MA, Bundy BN, Deppe G, et al. Cervical carcinoma metastatic to para-aortic nodes: Extended field radiation therapy with concomitant 5-fluorouracil and cisplatin chemotherapy: A Gynecologic Oncology Group study. *Int J Radiat Oncol Biol Phys* 1998;42:1015–1023. [PubMed: 9869224]
25. Grigsby PW, Heydon K, Mutch DG, et al. Long-term follow-up of RTOG 92–10: Cervical cancer with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2001;51:982–987. [PubMed: 11704321]
26. Borcoman E, Le Tourneau C. Pembrolizumab in cervical cancer: Latest evidence and clinical usefulness. *Ther Adv Med Oncol* 2017;9: 431–439. [PubMed: 28607581]
27. Zhang G, Fu C, Zhang Y, et al. Extended-field intensity-modulated radiotherapy and concurrent cisplatin-based chemotherapy for postoperative cervical cancer with common iliac or para-aortic lymph node metastases. *Int J Gynecol Cancer* 2012;22:1220–1225. [PubMed: 22854654]
28. Zhang G, He F, Fu C, et al. Definitive extended field intensity-modulated radiotherapy and concurrent cisplatin chemosensitization in the treatment of IB2–IIIB cervical cancer. *J Gynecol Oncol* 2014;25: 14–21. [PubMed: 24459576]
29. Boje N, Jensen K, Pötter R, et al. Bowel morbidity following radio-chemotherapy and image-guided adaptive brachytherapy for cervical cancer : Physician- and patient reported outcome from the EMBRACE study. *Radiother Oncol* 2018;127:431–439. [PubMed: 29880222]
30. Fokdal L, Pötter R, Kirchheiner K, et al. Physician assessed and patient reported urinary morbidity after radio-chemotherapy and image guided adaptive brachytherapy for locally advanced cervical cancer. *Radiother Oncol* 2018;127:423–430. [PubMed: 29784450]
31. Najjari Jamal D, Pötter R, Haie-Meder C, et al. Physician assessed and patient reported lower limb edema after definitive radio(chemo)therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: A report from the EMBRACE study. *Radiother Oncol* 2018;127:449–455. [PubMed: 29631933]
32. Smet S, Pötter R, Haie-Meder C, et al. Fatigue, insomnia and hot flashes after definitive radiochemotherapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: An analysis from the EMBRACE study. *Radiother Oncol* 2018;127: 440–448. [PubMed: 29627137]
33. Mell LK, Sirák I, Wei L, et al. Bone marrow-sparing Intensity Modulated Radiation Therapy with concurrent cisplatin for stage IB–IVA cervical cancer: An International Multicenter Phase II Clinical Trial (INTERTECC-2). *Int J Radiat Oncol Biol Phys* 2017;97:536–545. [PubMed: 28126303]
34. Wu ES, Oduyebo T, Cobb LP, et al. Lymphopenia and its association with survival in patients with locally advanced cervical cancer. *Gynecol Oncol* 2016;140:76–82. [PubMed: 26571200]
35. Cho O, Chun M, Chang S, Oh Y. Prognostic value of severe lymphopenia during pelvic concurrent chemoradiotherapy in cervical cancer. *Anticancer Res* 2016;36:3541–3547. [PubMed: 27354621]
36. Glicksman R, Chaudary N, Pintilie M, et al. The predictive value of nadir neutrophil count during treatment of cervical cancer: Interactions with tumor hypoxia and interstitial fluid pressure (IFP). *Clin Transl Radiat Oncol* 2017;6:15–20. [PubMed: 29594218]
37. Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: Final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet* 2017;390:1654–1663. [PubMed: 28756902]

Fig. 1.

Kaplan-Meier plots comparing IMRT/3D-IGABT versus 2D EBRT/BT outcomes for (A) regional control, (B) distant control, (C) freedom from relapse, (D) cancer-specific survival, and (E) overall survival. *Abbreviations:* IMRT = intensity modulated radiation therapy; 2D EBRT/BT = 2-dimensional external beam radiation therapy/brachytherapy; 3D-IGABT = 3-dimensional image-guided adapted brachytherapy.

Fig. 2.

Kaplan-Meier plots of freedom from relapse comparing IMRT/3D-IGABT versus 2D EBRT/BT for patients with (A) no FDG-avid nodes, (B) FDG-avid pelvic lymph nodes only, and (C) FDG-avid pelvic and paraortic nodes. Kaplan-Meier plots of CSS comparing IMRT/3D-IGABT versus 2D EBRT/BT for patients with (D) no FDG-avid nodes, (E) FDG-avid pelvic lymph nodes only, and (F) FDG-avid pelvic and paraortic nodes. *Abbreviations:* CSS = cancer-specific survival; FDG = fluorodeoxyglucose; IMRT = intensity modulated

radiation therapy; 2D EBRT/BT = 2-dimensional external beam radiation therapy/
brachytherapy; 3D-IGABT = 3-dimensional image-guided adapted brachytherapy.

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Fig. 3. Cumulative hazard plot of grade 3 or higher bowel or bladder late toxicities in the IMRT/3D-IGABT and 2D EBRT/BT groups. *Abbreviations:* B/B = bowel or bladder; IMRT = intensity modulated radiation therapy; 2D EBRT/BT = 2-dimensional external beam radiation therapy/brachytherapy; 3D-IGABT = 3-dimensional image-guided adapted brachytherapy.

Table 1

Patient and treatment characteristics

	2D EBRT/BT (n = 300)	IMRT/3D-IGABT (n = 300)	P value
Age (median y)	49 (23–88)	50 (24–88)	.45
Histology			.003
Squamous	270 (90%)	245 (82%)	
Nonsquamous	30 (10%)	55 (18%)	
Tumor PET volume (median mL)	47 (1–536)	31 (1–597)	< .001
FIGO stage			.10
IB1	33 (11)	40 (13)	
IB2	54 (18)	73 (24)	
IIA	6 (2)	6 (2)	
IIB	124 (41)	110 (37)	
IIIA	2 (1)	8 (3)	
IIIB	78 (26)	59 (20)	
IVA	3 (1)	4 (1)	
PET lymph nodes			.03
None	120 (40)	139 (46)	
Pelvis	137 (46)	112 (37)	
Pelvis and paraortic	34 (11)	46 (15)	
Pelvis, paraortic, and supraclavicular	9 (3)	3 (1)	
Chemotherapy	255 (85)	276 (92)	.007
Brachytherapy			< .001
2D	299 (99.7)	24 (8)	
3D-computed tomography	1 (0.3)	55 (18)	
3D-magnetic resonance imaging	0 (0)	221 (74)	
LDR brachytherapy	119 (40)	0 (0)	< .001
HDR brachytherapy	181 (60)	300 (100)	

Abbreviations: 2D = 2-dimensional; 2D EBRT/BT = 2-dimensional external beam radiation therapy/brachytherapy; 3D = 3-dimensional; 3D-IGABT = 3-dimensional image-guided adapted brachytherapy; FIGO = International Federation of Gynecology and Obstetrics; HDR = high-dose-rate; IMRT = intensity modulated radiation therapy; LDR = low-dose-rate; PET = positron emission tomography.

Table 2

Univariable and multivariable Cox regression for cancer-specific survival

Characteristic	Univariable hazard ratio (95% confidence interval)	Multivariable hazard ratio (95% confidence interval)
Age	1.000 (0.991–1.010), $P = .927$	-
Histology		-
Squamous	Reference	
Nonsquamous	0.985 (0.670–1.446), $P = .937$	
Tumor volume	1.002 (1.000–1.004), $P = .025$	Knocked out in multivariable model
FIGO stage		
I	Reference	Reference
II	1.500 (1.056–2.128), $P = .023$	1.316 (0.923–1.875), $PZ .129$
III–IVA	3.336 (2.361–4.715), $P < .001$	2.658 (1.861–3.795), $P < .001$
PET lymph nodes		
None	Reference	Reference
Pelvic	1.351 (0.989–1.844), $P = .058$	1.344 (0.983–1.838), $PZ .064$
Pelvic and paraortic	3.599 (2.523–5.132), $P < .001$	3.100 (2.162–4.447), $P < .001$
Pelvic, paraortic, and supraclavicular	13.431 (7.193–25.076), $P < .001$	11.524 (6.109–21.739), $P < .001$
IMRT/3D-IGABT (vs 2D EBRT/BT)	0.714 (0.546–0.933), $P = .014$	0.714 (0.544–0.937), $PZ .015$
LDR brachytherapy	Reference	-
HDR brachytherapy	0.802 (0.587–1.095), $P = .164$	
Chemotherapy	0.749 (0.515–1.089), $P = .131$	-

Abbreviations: 2D EBRT/BT = 2-dimensional external beam radiation therapy/brachytherapy; 3D-IGABT = 3-dimensional image-guided adapted brachytherapy; FIGO = International Federation of Gynecology and Obstetrics; HDR = high-dose-rate; IMRT = intensity modulated radiation therapy; LDR = low-dose-rate; PET = positron emission tomography.

Table 3

Grade 3 or higher late toxicities in the 2D EBRT/BT and IMRT/3D-IGABT groups

Complication	2D EBRT/BT (n = 300)	IMRT/3D-IGABT (n = 300)	Total (n = 600)
Rectovaginal fistula	12 (4)	12 (4)	24 (4)
Vesicovaginal fistula	12 (4)	7 (2.3)	19 (3.2)
Small-bowel obstruction	8 (2.7)	4 (1.3)	12 (2)
Cystitis (grade 4)	5 (1.7)	3 (1)	8 (1.3)
Large-bowel obstruction	5 (1.7)	1 (0.33)	6 (1)
Rectal ulcer	5 (1.7)	2 (0.67)	7 (1.2)
Rectal stricture	2 (0.7)	3 (1)	5 (0.8)
Ureteral stricture	4 (1.3)	1 (0.33)	5 (0.8)
Proctitis (grade 4)	2 (0.7)	0 (0)	2 (0.3)
Total	55 (18.3)	33 (11)	88 (14.7)

Abbreviations: 2D EBRT/BT = 2-dimensional external beam radiation therapy/brachytherapy; 3D-IGABT = 3-dimensional image-guided adapted brachytherapy; IMRT = intensity modulated radiation therapy.