Pulsed-dose-rate brachytherapy for uterine cervix carcinoma: 10 years of experience with 226 patients at a single institution

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ABSTRACT

PURPOSE: To analyze the long-term results of pulsed-dose-rate (PDR) brachytherapy (BT) in cervical carcinoma patients treated at a single institution.

METHODS AND MATERIALS: All patients with histopathologically proven Stages IB–IVA cervical carcinoma, treated at our institution with PDR intracavitary BT between April 1996 and November 2007, were included in this retrospective analysis. All patients underwent primary pelvic radiotherapy (45 Gy) with concomitant chemotherapy from 1999 and PDR intracavitary BT (16 Gy to the clinical target volume), followed by hysterectomy in 124 patients.

RESULTS: Two hundred twenty-six patients received radiochemotherapy and BT. With a median followup of 81.7 months, the 5-year overall survival, disease-free survival, and local control (LC) were 67%, 65%, and 80%, respectively; seventy-seven relapses were observed including 38 local recurrences. Multivariate analysis showed earlier FIGO (International Federation of Gynecology and Obstetrics) stage and absence of nodal involvement to be associated with better overall and disease-free survivals. Use of three-dimensional image-guided BT planning and absence of nodal involvement were associated with better LC in the multivariate analysis. Late Grade 3 toxicity was experienced by 22 patients (9.7%), consisting of gastrointestinal toxicity for 6 patients, urinary tract for 10 patients, lymphatics for 3 patients, and vaginal toxicity for 3 patients.

CONCLUSIONS: This study demonstrates excellent LC rates with few late side effects with PDR BT for cervix carcinoma, similar to those reported in the literature with historical standard low-dose-rate BT. © 2013 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: Pulsed-dose-rate brachytherapy; Cervical cancer; Image guided; Toxicity (side effects)

Introduction

Brachytherapy (BT) is an integral part of the treatment of cervical carcinomas, offering rapid dose falloff and very high conformational dose distribution in comparison with high-tech external beam irradiation. It offers a good therapeutic index with a high degree of local control (LC) and low toxicity (1–3). Continuous low-dose-rate (LDR) BT has been routinely used for the treatment of cervix carcinoma (1, 4), but high-dose-rate (HDR) BT was proposed as an alternative because of advantages of using a single-stepping source. Published oncologic results available for HDR are similar to LDR. At the beginning of the 1990s, pulsed-dose-rate (PDR) BT was developed combining isodose distribution optimization of HDR BT and radiobiologic advantages of LDR BT. Brenner and Hall (5) and Fowler and Van Limbergen (6) defined the conditions for equivalence of continuous to pulsed LDR BT. Since these publications, despite a lack of reported clinical results, PDR BT has been increasingly used in practice in France, replacing LDR.
Our experience using PDR intracavitary BT spans across 10 years involving more than 200 patients with over 5 years of followup for most patients. The aim of this clinical retrospective study was to present the results of this decade of experience at our institution for patients with cervical cancer.

Methods and materials

Patient and tumor characteristics

From April 1996 to November 2007, 226 patients with invasive carcinoma of the cervix were treated at our institution with PDR intracavitary BT with curative intent. All patients treated at our institution and for whom medical records were available were selected for inclusion in this retrospective study. Initial locoregional staging included a clinical evaluation performed by a gynecologic surgeon and radiation oncologist (according to the 1995 FIGO (International Federation of Gynecology and Obstetrics) classification (7)). Abdominopelvic MRI was obtained for 168 patients (74.3%) and CT imaging for 160 patients (70.8%). FDG-PET (fluorine-18-fluorodeoxyglucose positron emission tomography) scan was not systematically performed, and no decision has been taken based only on its results; 148 patients (65.4%), mostly Stages I and II, with a good health status and without suspicious lympho-aortic nodes at CT or MRI were selected to receive pelvic lymphadenectomy by coelioscopy first. Only 1 patient had a para-aortic lymphadenectomy. Nodal involvement was determined if histologically proven (65 patients) or suspected on CT (24 patients). All patients with positive lymph nodes, including IB1 stage, received first external beam radiation therapy and are included in the study. Stage IB1 patients treated with preoperative intracavitary PDR BT followed with colposohysterectomy were excluded from the analysis (19 patients). Institutional review board approval was obtained for this study, and it was conducted in compliance with the Helsinki Declaration.

Treatment characteristics

All patients received 45 Gy pelvic external beam radiotherapy (EBRT) before PDR BT with a standard four-field technique (190 patients) or a two anterior/posterior opposing fields technique (36 patients) using high mega-voltage photons from a linear accelerator (photons × 18 and 25 MeV). EBRT included the para-aortic area when the CT showed enlarged common iliac or para-aortic nodes. When the nodal involvement was histologically proved or suspected on CT, a complementary boost irradiation was delivered after BT to reach a minimum of 60 Gy to the parametria and/or involved pelvic nodes and 55 Gy to the para-aortic nodes, taking into account the dose contribution of BT. From 1999, based on the results of randomized trials (8–12), chemotherapy was given during EBRT for all stages ≥IB2, with intravenous cisplatin 40 mg/m² once a week for 5 weeks in 150 of 226 patients (66.4%). Chemotherapy courses were not delivered during the hospitalization for the BT procedure.

PDR-BT procedure and treatment planning

After EBRT, the PDR BT boost was delivered during a single hospitalization, using the PDR Selectron (Elekta, Stockholm, Sweden). At the beginning of the BT procedure, a careful clinical examination was carried out under general anesthesia to assess clinical response to EBRT. A Fletcher applicator was used, and no patient underwent interstitial BT. Pulses were delivered hourly during night and day. Before 1999, the BT treatment planning dosimetry was based on orthogonal radiographs, in accordance with International Commission on Radiation Units (ICRU) 38 (13). The prescribed dose was 16 Gy after radiochemotherapy. The dose was reported according to the ICRU38 guidelines with the 60 Gy isodose, total reference air kerma (TRAK), and dose to critical organs (bladder and rectal reference points). The dose distribution was calculated on orthogonal films for 68 patients. Three-dimensional (3D) computerized-assisted treatment based on CT (CT-based 3D PDR BT) was adopted for treatment of cervical cancer since 1999 and was carried out for 158 patients. CT at BT was performed with CT–MRI compatible Fletcher applicator in place and with intravenous contrast except in cases of renal insufficiency or allergy. Clinical target volume (CTV) and organs at risk (OARs) (rectum, sigmoid, bladder, and small bowel) were delineated. CTV corresponded to the high-risk (HR) CTV of the Brachytherapy Group of the European Society for Therapeutic Radiology and Oncology (GEC ESTRO) guidelines (14) and included the whole cervix and any palpable or macroscopic residual disease. The BT dose was prescribed on the target (HR CTV of GEC ESTRO). The dose was calculated on minimal peripheral dose of the target, and the dose rate prescribed was around 65 cGy/h that we have used previously. Care was taken to obtain a similar TRAK to that used previously with LDR BT. Concerning the OAR, no consensus and guidelines were established in 1999; at the date, we began CT-based 3D PDR BT. Dose in a low volume had been suggested to be well correlated with dose at OAR, and a value of 3 cm³ was chosen. The dose—volume constraints were dose—volume histograms (DVHs) 3 cm³ bladder ≤65 Gy (dose cumulated external irradiation EBRT + BT not calculated in EQD2 [equivalent dose in 2-Gray fractions]) and DVH 3 cm³ rectum ≤70 Gy. These doses were extrapolated out of our experience with LDR with doses calculated to the ICRU points (bladder and rectum reference points). The dose—volume constraints evolved with current practices and after 2005; the doses were calculated according to GEC ESTRO recommendations on dose reporting (24 patients). Until 2005, dose optimization was performed using only dwell positions, modifications only in the number of dwell positions in the uterine probe and number and position of the dwell positions in the ovoids. After 2005, graphical optimization was used (24 patients).
Surgery

According to the institutional gynecologic protocols, a surgical procedure was decided for FIGO IB2–II tumors with clinical assessment and MRI evaluation at the dose of 45 Gy, if the response to chemoradiation was less than 50%, for adenocarcinomas, in cases with initial extension to the endometrium, or in cases in which BT treatment was considered as nonoptimal. This surgical procedure consisted in a radical colpoplastectomy or an extrafacial hysterectomy. A pelvic lymph node dissection was performed at the time of hysterectomy if not previously carried out during the staging procedure: This had affected 16 of the 124 patients who underwent surgery after BT. In 14 cases, patients were referred to our center for BT after radiation therapy and did not receive an initial nodal staging procedure. In two cases, patients had a nonresectable node during the staging procedure which could be removed during the time of hysterectomy. Of the 16 final lymphadenectomies, 6 were positive and patients received a complementary boost of external irradiation on the involved removed nodes.

Followup and statistical analysis

Patients were followed every 4 months for the first year after treatment and then every 6 months until 5 years. Thereafter, followup was done annually. Primary end points were overall survival (OS) and disease-free survival (DFS), and LC calculated from the date of diagnosis by the Kaplan–Meier method (15). Events taken into account for OS were death of any cause, and for DFS relapses across all sites were taken into account. LC was assessed at clinical examination and defined as absence of local recurrence (centropelvic, lateropelvic, or vaginal). Locoregional recurrences included local and pelvic nodes recurrences. Lomboaortic metastatic nodes were considered to be metastatic relapse. Median followup was calculated with the reverse Kaplan–Meier method.

Univariate analysis, taking into account age (<40 years), FIGO stages (I and II vs. III and IV), nodal involvement (pathologically staged and radiologically involved nodes), histologic type, surgery, concomitant chemotherapy, and response to chemoradiation as predictive factors for OS and DFS, was performed using a log-rank test. For LC, 3D planning BT and BT dose prescription (D100 HR CTV [EQD2 (10)] >15.8 Gy) were also analyzed. All variables significant at \( p < 0.05 \) were then included in a multivariate analysis with a Cox proportional hazards model using the stepwise ascending method of maximum likelihood after verification of data proportionality.

The secondary end point was analysis of complications which were graded retrospectively using the Common Terminology Criteria of Adverse Events (CTCAE v3.0). Because of the difficulties in estimating low-grade toxicities in retrospective studies, we focused on Grades 3 and 4 toxicity, although grades for all side effects were identified. “Delayed or late” toxicities were defined as all toxicities occurring after 6 months. Toxicities were compared using Pearson’s \( \chi^2 \) across treatment characteristics (surgical procedure, adjunction of chemotherapies, dose of EBRT, external irradiation technique, technical modalities of EBRT, and laparoscopic lymphadenectomy). Across DVH to bladder and rectum, toxicities were compared using a Mann–Whitney test.

Results

Patient, tumor, and treatment characteristics

These characteristics are listed in Tables 1 and 2. Median patient age was 52 years (range, 26–82 years). The median pelvic dose was 45 Gy in 25 fractions, 5 days a week. Fifty-one patients underwent a complementary external irradiation boost (parametria and/or pelvic lymph nodes) with a median dose of 9 Gy (range, 8–10 Gy). The median dose for the PDR intracavitary boost was 16 Gy. From the beginning of EBRT to the PDR BT procedure, the median time was 49 days (range, 30–91 days). A surgical procedure was performed after PDR BT boost for 124 patients. Surgery was performed mainly in Stages I and II patients (117 of 124) and 61.3% of Stages I and II patients overall received complementary surgery (117 of 191). The details of the surgical indications are presented in Table 2. Only 27 operated patients (21.7%) were in complete pathologic remission.

Outcomes and survival

The median followup for all patients was 81.7 months (6.8 years) (95% confidence interval [CI], 69.8–73.5). A total of 77 failures were observed with 18.6 months (range, 4.9–71.8 months) median time of occurrence. Metastatic,
locoregional, and local recurrences occurred for 62 (27.4%), 41 (18.1%), and 38 (16.8%) patients, respectively. Among the 41 locoregional recurrences, 36 occurred within the treated volume. The median delay to local relapse was 13 months (range, 5–71.8 months). Among the 62 patients with metastatic failures, 36 were free of locoregional failure during followup.

At 5 years, OS was 67% (95% CI, 0.60–0.73), DFS was 65% (95% CI, 0.58–0.71), and LC was 80% (95% CI, 0.74–0.85). OS, DFS, and LC are detailed according to FIGO stages in Figs. 1–3.

Univariate analysis showed that more advanced FIGO stage (p = 0.007, p = 0.001, and p = 0.006) and nodal involvement (p = 0.001, p < 0.0001, and p < 0.0001) were predictive of poorer LC and shorter DFS and OS, respectively. Age, histology, concurrent chemotherapy, consolidation surgery, and response to chemoradiation were not significant. Multivariate analysis confirmed the relationship between shorter OS and DFS with more advanced FIGO stage (hazard ratio, 1.8; 95% CI, 1.09–3.17), p = 0.02 (hazard ratio, 2.71; 95% CI, 1.18–3.37), p = 0.009 and nodal involvement (hazard ratio, 2.0; 95% CI, 1.3–3.2), p < 0.0001 (hazard ratio, 2.7; 95% CI, 1.7–4.3), p < 0.001, respectively. In univariate analysis, FIGO smaller stages (I and II), negative nodes, and use of 3D BT planning were predictive of better LC p = 0.012, p = 0.001, and p = 0.003. TRAK 1.2 (p = 0.37), complementary surgery (p = 0.09), and BT dose D100 HR CTV >15.8 [EQD2 (10)] Gy (p = 0.71) were not significant.

For LC, multivariate analysis confirmed the significance of nodal involvement (p < 0.0005; hazard ratio, 3.2; 95% CI, 1.6–6.3) and use of 3D imaging-guided BT planning (hazard ratio, 2.3; 95% CI, 1.22–4.53; p = 0.01). Early FIGO stages were not associated with better LC in the multivariate model (p = 0.12). Comparisons with nonparametric Wilcoxon test were done to try to explain this statistical benefit of 3D dosimetry in LC. There is
no statistical difference of volume of the isodose 60 Gy between patients treated used two-dimensional (97.8 cc; range, 17.1–337.5) and 3D (95.8 cc; range, 43.2–326.2) dosimetry plan \((p = 0.7)\). Alike, doses to point A \((p = 0.29)\) and TRAK \((p = 0.45)\) were not statistically different in these two groups.

**Toxicity**

Side effects are reported in Table 3. Of the 226 patients, only 22 (9.7%) presented with delayed Grade 3 complications. Most patients developed only one Grade 3 toxicity \((n = 14)\). Seven patients developed two Grade 3 toxicities and 1 patient developed three Grade 3 toxicities. Six patients (2.6%) had gastrointestinal tract complications and 10 patients (4.4%) had severe urinary tract toxicity (Grade ≥3). Three patients (1.3%) experienced complete obliteration of the whole vagina (Grade 3). Finally, 123 patients presented Grades 1 and 2 late vaginal side effects (dryness, atrophy of the vaginal epithelium, partial synechiae, or stenosis of the upper vagina). No statistically significant increase in delayed Grade ≥3 toxicities was observed for any treatment characteristics (EBRT dose < 45 vs. ≥45 Gy, two-field vs. four-field technique, surgery or not, pelvic lymphadenectomy, and concurrent chemotherapy). Dose delivered to 3 cm³ \((p = 0.01)\) or 5 cm³ \((p = 0.03)\) bladder was significantly higher in the group of patients presenting Grade ≥3 urinary complications.

**Discussion**

With 226 patients and a median followup of over 6.8 years, the present study represents one of the largest series published in PDR BT. With 5-year LC of 85.3% for Stages I and II, 71.4% for Stages III and IV, and 9.7% for Grade ≥3 late toxicity, our results compare favorably with the published reports. Swift et al. (16) reported clinical results of 65 patients with pelvic malignancies (42 patients with primary cervical carcinoma) treated with PDR BT with dose per pulse of 40–80 cGy/h. With a median followup of 15.1 months, the incidence of Grade ≥3 acute complications was 6.5%, which was not higher than that with standard continuous LDR. They attributed their low rate of complications to the isodose optimization capabilities of PDR BT. Rogers et al. (17) reported outcomes for a retrospective cohort of 46 patients with cervical carcinoma treated with PDR BT. With a median followup of 25 months, the overall 4-year DFS rate was 66% for the entire group, 100% for Stage IB, 69% for Stage II, and 68% for Stages III and IV. The 4-year actuarial complication-free survival rate for Grade ≥3 complications was 93%. More recently, Rath et al. (18) reported the results of a retrospective study of 48 patients treated with PDR intracavitary BT for cervical carcinoma. With a median followup of only 15 months, cumulative recurrence-free survival for all patients, Stages I and II, and Stages III and IV was 80%, 82%, and 78%, respectively.

The PDR afterloading system has advantages; when compared with previous LDR afterloading systems such as source preparation and inventory are not needed, there is only one source to replace every 3 months, and dosimetry optimization and both intracavitary and interstitial brachytherapies are feasible. Indeed, for a given source strength, the dose rate may be adjusted by modifying dwell times and/or pulse intervals to optimize dose distribution. HDR BT has the same advantages, using a single-stepping source. Nevertheless, according to radiobiologic considerations, the therapeutic ratio will be greater for LDR. Several studies compare LDR BT as standard treatment vs. HDR
BT, with some contradictory results. A recent meta-analysis pooled the results of randomized studies and concludes no significant differences for survival and LC (19).

In interpreting these results, it is necessary to keep in mind the range of radiation and BT technologies used in these studies. PDR seems to be a good compromise between LDR and HDR with radiobiologic advantages of LDR and technical advantages of HDR. Only one prospective study has compared continuous LDR BT and PDR BT for cervical carcinoma: 166 patients were analyzed prospectively, 57 in the PDR BT arm. The dose rate was similar in both groups (66 cGy/h in LDR and 70 cGy/h in PDR arm). No differences were found for severe late toxicity. The actuarial 3-year OS rate was 75% for both groups, with no significant differences in 3-year DFS for the PDR BT group (70% vs. 57%, \( p = 0.19 \)) (20).

Only one randomized prospective study suggests the impact of LDR variations (21), with 204 patients with Stage I and limited Stage II cervical cancer randomized to receive one of two preoperative BT LDRs (0.4 and 0.8 Gy/h). The investigators reported a greater late complications rate with higher dose rate (38 cGy/h vs. 73 cGy/h), with no impact on survival. Our results do not support this finding as we find a low complication rate with a median dose rate of 65 cGy/h: 2.6% of gastrointestinal tract complications, 4.4% urinary tract severe toxicity, and 1.3% complete obliteration of the vagina. These toxicity rates were in accordance with those established with LDR. In the review by Barillot et al. (22), 4% of late severe urinary toxicity and 2–4% of gastrointestinal tractus (35% for locally advanced cancer) were established. We acknowledge the limitations of this study owing to its retrospective assessment of toxicity; however, with 50.6% Grades 1 and 2 late vaginal effects, our rate is less than that reported by Potter et al. (23) in a large series of HDR BT (78%).

In the multivariate analyses on outcomes, classical clinical factors such as negative nodal involvement are correlated with the 5-year LC but also the use of 3D-based planning BT. Interest in BT 3D imaging planning has increased and represents currently one of the most important developments in gynecologic BT. Recently, guidelines have been published by the GEC ESTRO (14, 24). However, up until now, limited clinical evidence has been published demonstrating the impact of 3D BT. Chârargari et al. (25) have been the first to report their experience with MRI-based intracavitary PDR BT so far, for 45 patients with locally advanced cervical carcinoma. The 2-year OS was 78% without any Grade 4 toxicity and with only one Grade 3 toxicity with a vesicovaginal fistula. The results of the Vienna Group which studied MRI-based 3D HDR BT (26) showed that improved treatment outcomes with optimized 3D planning were achievable for patients with larger target sizes of >5 cm.

Recently, in a retrospective analysis, Kang et al. (27) showed that the use of CT-based 3D BT resulted in a significant decrease of severe late rectal bleeding and in an improvement of LC for patients with tumor size >4 cm. In a retrospective series including 84 patients with primary locally advanced cervical carcinoma, Haie-Meder et al. (28) suggest that applying individual treatment planning with 3D MRI-guided LDR BT is feasible and efficient in routine clinical practice and should become the standard modality of gynecologic BT.

In 2006, A French prospective multicentric study STIC PDR (Programme de Soutien aux Techniques Innovantes Cœutues Pulsed Dose Rate) was initiated for patients treated for cervix carcinoma comparing a PDR BT method based on orthogonal x-rays (two-dimensional group) or based on 3D imaging (3D group). Their results in the 3D arm at 2 years (LC, locoregional control [LRC], and DFS) are relatively similar to ours at 5 years for the two groups of patients with surgery or not (29). For the group with surgery, 2-year LC was 93% vs. 5-year LC was 86.3%, 2-year LRC was 88.6% vs. 5-year LRC was 84%, and 2-year DFS was 77.1% vs. 5-year DFS was 68.3% in our series. For the group without surgery, 2-year LC was 78.5% vs. 5-year LC was 79.4%, 2-year LRC was 69.6% vs. 5-year LRC was 75%, and 2-year DFS was 60.3% vs. 5-year DFS was 60% in our series. Preliminary dosimetric data are published for the first 637 patients: in the 3D arm, concerning the 267 patients treated after EBRT with or without complementary surgery, \( D_{100} \) HR CTV is 10.8 and 16.6 Gy; \( D_{90} \) HR CTV is 17.9 and 26.8 Gy (30), respectively. Our retrospective study allows us to compare only the \( D_{100} \) HR CTV \([\text{cm}^3 \text{EQD}_2 (10)]\) in the group with surgery, our \( D_{100} \) HR CTV was 15.8 Gy \([\text{cm}^3 \text{EQD}_2 (10)]\) vs. 10.8 Gy \([\text{cm}^3 \text{EQD}_2 (10)]\) (STIC PDR). In the group without surgery, our \( D_{100} \) HR CTV was quite similar (16.85 Gy) \([\text{cm}^3 \text{EQD}_2 (10)]\) vs. 16.6 Gy \([\text{cm}^3 \text{EQD}_2 (10)]\) (STIC PDR) (30). In these two series, the \( D_{100} \) HR CTV \([\text{cm}^3 \text{EQD}_2 (10)]\) was lower than GEC ESTRO recommendations (14). Dimopoulos et al. (26) obtained an increase in LC rates of 95% if the \( D_{90} \) biologically equivalent dose HR CTV was 87 Gy \([\text{cm}^3 \text{EQD}_2 (10)]\) for patients without surgery. Treatment policy in our series was individually tailored according to disease characteristics and response to chemoradiation. Despite the low dose level delivered, the 5-year LC rate was comparable with traditional LDR BT studies (79.4% for patients without surgery) even if recent 3D series relate higher LC with generally more advanced tumors. As example, Pötter et al. (31) related 3-year LC rate of 95% for more advanced with 7.7% Grades 3–4 late complications. Haie-Meder et al. (28, 31) reported a 2-year LC rate of 89.2% with low Grade 3 delayed toxicity (4.7%). Tan et al. (32) in a series of 28 patients treated between 2005 and 2007 with CT-based guided HDR BT relate 3-year LC of 96%, with an overall actuarial risk of serious late morbidity of 14%. Nevertheless, it raises the question of whether the dose should be escalated to get better LC with a tolerable complications rate. On the other hand, for nonresponders, patients presenting with extensive disease, dose escalation with image-based optimization BT and use of additional interstitial BT could be the best treatment (33).
Conclusions and future implications

Considering the advantages of PDR BT, the present data support PDR BT for the treatment of cervical cancer with similar results to LDR BT in LC rates and few late side effects. Our results indicate that this technique may be used to replace standard LDR BT. The clinical impact of 3D-based planning BT is demonstrated in this study, with statistically significant better LC and should become the standard for current gynecologic BT. The American Brachytherapy Society published in 2012 guidelines concerning LDR and PDR BT and recommended adoption of GEC ESTRO recommendations and image-based treatment planning (34). A dose escalation study in PDR BT with optimized dosimetry based on MRI is currently underway with the Tridico French cooperative trial and the GEC ESTRO multidimensional European observational study of MRI-guided BT, “EMBRACE,” should also bring further supporting data for this method.

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