Results from chemoradiotherapy for squamous cell cervical cancer with or without intracavitary brachytherapy

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Abstract

Purpose: The aim of this study is to compare the outcomes of intracavitary high-dose-rate brachytherapy (BT-IC) boost and external beam radiotherapy (EBRT) boost in patients treated with concomitant chemoradiotherapy for squamous cell carcinoma of the cervix.

Material and methods: It is a retrospective review of 92 patients with stage IB1-IVA cervical cancer treated with concomitant chemoradiotherapy between 2008 and 2013. All patients received pelvic 3D conformal EBRT (range, 45-50.4 Gy) concomitant with weekly cisplatin (40 mg/m²), and a BT-IC boost (37 patients: 4 fractions of 6 Gy prescribed to a point A) to the tumor or a 3D conformal EBRT boost (55 patients: 16.2 Gy), if the former was not technically feasible.

Results: The 5-year overall survival and recurrence-free survival rates for both groups were 68% and 55%, respectively. The 5-year overall survival and recurrence-free survival were better and statistically significant in the BT-IC group with 82% and 79%, respectively, as compared to the EBRT group with 58% and 38%, respectively. In multivariate analysis controlling for maximum tumor dimension, lymph node status, and FIGO stage, EBRT boost was associated with a statistical significant increase in the risk of recurrence (HR: 3.56; 95% CI: 1.27-10.02; \( p = 0.016 \)) and a trend towards an increase in the risk of death (HR: 3.14; 95% CI: 0.97-10.17; \( p = 0.056 \)). Lymph node status was also significantly associated with a greater risk of recurrence.

Conclusions: BT-IC boost was associated with a lower recurrence rate and better overall survival and recurrence-free survival. EBRT boost patients had a three-fold increase in the risk of recurrence. Brachytherapy is essential in the treatment of cervical cancer and improved alternatives are needed for patients who are not candidates for standard brachytherapy applicators.

Key words: high-dose-rate brachytherapy, cervical cancer, gynecological cancer, radiotherapy.

Purpose

Radiotherapy (RT) with concomitant chemotherapy is considered the standard treatment for locally advanced cervical cancer, and this treatment combination was compared to RT alone in randomized trials and showed an improved survival [1,2,3,4]. Guidelines recommend a combined RT treatment with external beam radiotherapy (EBRT) to the pelvis and intracavitary brachytherapy (low-, pulsed-, or high-dose-rate) boost to the tumor [5,6]. Intracavitary brachytherapy (IC-BT) allows for a highly conformal hypofractionated boost increasing the total tumor dose to over 80 Gy of 2 Gy equivalent dose (EQD2), while maintaining acceptable doses to the nearby organs at risk. Large national databases and individual center retrospective reviews have suggested a benefit in outcomes when EBRT is combined with IC-BT [7,8,9,10,11,12,13,14].

However, IC-BT is sometimes not technically possible, due to large tumor volume that cannot be fully covered without excessive toxicity to the organs at risk or difficulties concerning the technique, including an insertion of the intrauterine tandem. In such cases, EBRT tumor boost is given, usually up to 66 Gy. Because EBRT boost is not the ideal solution, the role of interstitial brachytherapy is recently growing in the treatment of locally advanced tumors. The objective of this study was to compare the outcomes of patients treated with or without IC-BT boost at our department.

Material and methods

Patient population

This series includes 92 patients with histological diagnosis of squamous cell carcinoma of the cervix, treated...
with concomitant chemoradiotherapy between 2008 and 2013 at a single radiotherapy department.

In 37 patients, pelvic EBRT was combined with a BT-IC boost. The remaining 55 patients were treated only with EBRT because of technical feasibility. They received an EBRT boost to the tumor. The data was collected retrospectively from an investigation of patients records.

**Diagnosis and staging**

All patients underwent vaginal inspection, bimanual palpation, transvaginal ultrasound evaluation, and biopsies of the tumor. Most patients underwent radiological staging, usually a chest and abdomen contrast-enhanced computed tomography (CT) scan together with a gadolinium contrast-enhanced pelvic magnetic resonance imaging (MRI). Staging was completed in combination with clinical observation and radiological studies according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system.

**Brachytherapy**

BT-IC boost was given using a high-dose-rate iridium-192 ($^{192}$Ir) source afterloader, with an intrauterine tandem and ring applicator set. Four fractions of 6 Gy were prescribed to point A, in most cases weekly, after the completion of pelvic EBRT. It was not possible to give the full four fractions to all patients receiving BT-IC boost due to technical application constraints, usually difficulties in inserting the intrauterine tandem because of radiation stenosis of the cervical os or perforation (uterine or cervical). In those cases, an EBRT boost was given to complete the dose to the tumor. All patients who had at least one BT-IC fraction were included in the BT-IC group.

**External beam radiotherapy**

EBRT was given with 3D conformal radiotherapy (3D-CRT), using a linear accelerator with photon energies > 6 MV. CT simulation was made with a void rectum and filled bladder. All patients received pelvic field EBRT, with a clinical target volume (CTV) encompassing the tumor, cervix, uterus, upper third of the vagina, parametrial tissue, and regional lymph nodes (obturator, external iliac, internal iliac, presacral nodes, and common iliac nodes up to the level of L4-L5), with a median dose of 50.4 Gy (range, 45-50.4 Gy) in 1.8 Gy once-daily fractions. In case of clinically suspicious paraaortic lymph nodes detected on imaging, patients received paraaortic lymph node irradiation up to the level of T12-L1. If parametrical invasion was clinically palpable or detectable in imaging, patients who received the BT-IC boost were given a parametrical boost up to 16.2 Gy at the discretion of treating physician. The parametrical boost was only delivered after all brachytherapy applications to consider the dose already received to point B. In the EBRT only group, patients received a new treatment plan, with repeated CT simulation and clinical examination in the last week of treatment. The new CTV encompassed only the tumor, cervix, and uterus, with a median dose of 16.2 Gy.

### Table 1. Patient and treatment characteristics of both treatment groups

|                          | Brachytherapy (n = 37) | EBRT (n = 55) | P     |
|--------------------------|------------------------|---------------|-------|
| **Patient**              |                        |               |       |
| Age, mean (years)        | 53.7                   | 53.4          | 0.903 |
| MTD                      | 39.4                   | 52.6          | < 0.0001 |
| **FIGO stage (%)**       |                        |               |       |
| IB1                      | 1 (2.7)                | 0             | 0.004 |
| IIA1                     | 2 (5.4)                | 0             |       |
| IIA2                     | 3 (5.5)                |               |       |
| IIB                      | 32 (86.5)              | 31 (56.4)     |       |
| IIIA                     | 1 (2.7)                | 4 (7.3)       |       |
| IIIIB                    | 1 (2.7)                | 14 (25.5)     |       |
| IVB                      | 0                      | 3 (5.5)       |       |
| **FIGO stage (%)**       |                        |               | < 0.0001 |
| ≤ IIB                    | 35 (94.6)              | 34 (61.8)     |       |
| > IIB                    | 2 (5.4)                | 21 (38.2)     |       |
| **Lymph nodes (%)**      |                        |               | 0.161 |
| Yes                      | 7 (18.9)               | 18 (32.7)     |       |
| No                       | 30 (81.1)              | 37 (67.3)     |       |
| **Lymph node location (%)** |                       |               | 0.355 |
| Pelvic                   | 5 (71.4)               | 8 (42.1)      |       |
| Paraaortic               | 1 (14.3)               | 1 (5.3)       |       |
| Both                     | 1 (14.3)               | 9 (47.4)      |       |
| **Treatment**            |                        |               |       |
| Pelvic EBRT dose (mean)  | 49.7                   | 50.3          | 0.051 |
| Parametric EBRT (%)      |                        |               | 0.306 |
| Yes                      | 2 (5.4)                | 8 (14.5)      |       |
| No                       | 35 (94.6)              | 47 (85.5)     |       |
| Parametric EBRT boost (%)|                        |               |       |
| Yes                      | 26 (70.3)              |               |       |
| No                       | 11 (29.7)              |               |       |
| Boost EBRT dose (mean)   | 10.5                   | 16.2          | < 0.0001 |
| Number of BT-IC fractions given (6 Gy) |           |               |       |
| 1                        | 2 (5.4)                |               |       |
| 2                        | 3 (8.1)                |               |       |
| 3                        | 2 (5.4)                |               |       |
| 4                        | 30 (81.1)              |               |       |
| BT-IC dose (mean)        | 21.7                   |               |       |
| Total EQD2 dose (mean)   | 79.9                   | 65.8          | < 0.0001 |
| Total BED dose (mean)    | 95.9                   | 78.9          | < 0.0001 |
| Treatment time (days)    | 78                     | 58.9          | < 0.0001 |

*EBRT – external beam radiation therapy, BT-IC – intracavitary brachytherapy, FIGO – International Federation of Gynecology and Obstetrics, MTD – maximal tumor dimension*
The overall recurrence rate for both groups was 34.8% 
(n = 37). The EBRT boost group had a significantly higher 
recurrence rate compared to the BT-IC group (49.1% vs. 
13.5%; p = 0.001) (Table 2). Most recurrences were local in 
both groups and more frequent in the EBRT group (37.5% vs. 
12.5%). Paraortic lymph node recurrences were de-
tected only on the EBRT group, in 15.6% of cases. Distant 
recurrences were rare in the BT-IC group compared to 
the EBRT group (3.1% vs. 31.3%). Patients with clinically 
suspicious lymph nodes at diagnosis had a higher rate of 
recurrence compared to patients without regional disease 
(72% vs. 20.9%; p < 0.0001). Most patients with positive 
lymph nodes developed distant recurrences (56.3%).

Treatment time and total treatment dose
Treatment time in the BT-IC group included all radio-
therapy treatment, like pelvic EBRT, brachytherapy ap-
lications, and the boost to parametrial tissue if indicat-
ed, resulted in a longer overall treatment time compared 
with the EBRT only approach (78 days vs. 58.9 days; 
p < 0.0001) (Table 1).

Total treatment dose converted to EQD2 and BED 
was significantly higher in the BT-IC group compared 
with the EBRT only group (EQD2: 79.5 Gy vs. 65.8 Gy; 
p < 0.0001) (BED: 95.9 Gy vs. 78.9 Gy; p < 0.0001).

Survival
Median follow-up time for all patients was 67 months 
(range, 5-144 months).

The 5-year overall survival (OS) rate for both groups 
was 68%. The BT-IC group had a statistically significant 
superior 5-year OS (82% vs. 58%; log-rank p = 0.005) (Fig-
ure 1). Mean time for recurrence was 21.3 months. The 
5-year recurrence-free survival (RFS) rate was 55% for 
both groups. The BT-IC group had also a superior 5-year 
RFS compared to the EBRT group (79% vs. 38%; log-rank 
 p = 0.0001) (Figure 2).

On multivariate Cox proportional regression analysis 
for RFS when controlling for maximal tumor dimension 
and FIGO stage, both clinically positive lymph node dis-
ease and treatment group (HR: 3.56; 95% CI: 1.27-10.02; 
p = 0.016) were statistically significant prognostic factors 
(Table 3). On multivariate analysis for OS, FIGO stage 
(≤ IIB vs. > IIB) was a significant prognostic factor, where-
as the treatment group displayed a clear trend towards an increase in the risk of death (HR: 3.14; 95% CI: 0.97-10.17; p = 0.056).

A further multivariate analysis included only patients with FIGO stage ≤ IIB from both treatment groups (EBRT 34 patients; BT-IC 35 patients). On multivariate Cox regression for RFS, the treatment group remained a statistical significant prognostic factor (Table 4), but not on multivariate regression for OS. Both lymph node status and maximal tumor dimension were not statistically significant in the analysis.

### Table 3. Multivariate Cox proportional regression analysis for recurrence-free survival and overall survival

|                | Multivariate Cox regression on RFS | Multivariate Cox regression on OS |
|----------------|-----------------------------------|----------------------------------|
|                | HR  | 95% CI | P       | HR  | 95% CI | P       |
| Stage ≤ IIB vs. > IIB | 0.693 | 0.302 | 1.59 | 0.347 | 0.136 | 0.885 | 0.027 |
| Lymph nodes Negative vs. positive | 0.371 | 0.177 | 0.78 | 0.009 | 0.579 | 0.241 | 1.387 | 0.22  |
| MTD Negative vs. positive | 0.999 | 0.968 | 1.031 | 0.93  | 0.999 | 0.968 | 1.031 | 0.93  |
| Boost EBRT vs. BT | 3.564 | 1.268 | 10.02 | 0.016 | 3.14  | 0.969 | 10.171 | 0.056 |

MTD – maximal tumor dimension, EBRT – external beam radiotherapy, BT – brachytherapy

### Table 4. Multivariate Cox proportional regression analysis for recurrence-free survival and overall survival on patients with FIGO stage ≤ IIB

|                | Multivariate Cox regression on RFS | Multivariate Cox regression on OS |
|----------------|-----------------------------------|----------------------------------|
|                | HR  | 95% CI | P       | HR  | 95% CI | P       |
| Lymph nodes Negative vs. positive | 0.466 | 0.181 | 1.2 | 0.114 | 0.466 | 0.181 | 1.2 | 0.114 |
| MTD Negative vs. positive | 1.023 | 0.994 | 1.052 | 0.121 | 1.023 | 0.994 | 1.052 | 0.121 |
| Boost EBRT vs. BT | 3.087 | 1.047 | 9.102 | 0.041 | 3.087 | 1.047 | 9.102 | 0.041 |

MTD – maximal tumor dimension, EBRT – external beam radiotherapy, BT – brachytherapy
Discussion

The 5-year OS rate (68%) was higher than in other published series, especially the OS rate in the BT-IC group (82%). As for the EBRT boost group OS results, although they were significantly lower than in the BT-IC group (58%), the outcomes are still higher compared to other published results. Two Japanese groups reported their outcomes on patients treated with an EBRT boost, with a corresponding 3-year OS rate of 43.8% [15] and 2-year OS rate of 43% [16].

Possible contributions to these positive outcomes are the lower median age of the patient population (53 years), the use of concurrent chemotherapy in all patients, and the predominance of lower FIGO stage (≤ IIIB).

Limitations of our study included its retrospective nature and differences in tumor size and FIGO stage between groups. As it was expected, most patients from the EBRT boost group had larger tumors and/or more advance disease at diagnosis, precluding them from BT-IC. Also, some patients could receive only one to three fractions of BT-IC of the four prescribed, and completed the dose with EBRT. These patients were included in the BT-IC group, possibly resulting in bias regarding their outcome. In an attempt to minimize such biases, multivariate Cox regressions were performed, with maximal tumor dimension and FIGO stage as factors to decrease their contribution to RFS and OS outcomes. As the number of patients with lower FIGO stage was similar between groups, an additional analysis was performed only for patients with FIGO stage ≤ IIIB. In both cases, the treatment group was a significant prognostic factor in terms of RFS, with a three-fold increase in the risk of recurrence. When all patients were considered, there was borderline statistical significance in the risk of death between EBRT and BT-IC.

Lanciano et al. reported results from patterns of care studies from the 70’ demonstrating a benefit for BT-IC in terms of pelvic control and survival [7]. Longson et al. published a retrospective review of 983 FIGO IIBB patients, also showing a benefit for BT-IC in terms of disease-free survival [8].

Karlsson et al. reviewed 220 patients, of which 134 had received a BT-IC boost, whereas 86 patients received EBRT boost alone. The 5-year OS and cancer-specific survival rates were 42.5% and 55.5%, respectively, and all types of survival were better for patients receiving BT-IC [11].

Both groups had significant differences in total treatment time and total treatment dose. It is established that a shorter treatment time correlates with better outcomes [17,18,19], and an overall treatment duration within 8 weeks (56 days) is currently recommended [5,20]. Shorter treatment time in the EBRT boost group (58.9 vs. 78 days) is expected, since the BT-IC boost was usually performed after completing pelvic EBRT. It is then reasonable to assume that the addition of BT-IC boost is more relevant than the overall treatment time, when considering boost approaches. Nevertheless, we have more recently changed our treatment protocol, starting an BT-IC boost application before the completion of pelvic EBRT to shorten the overall treatment time.

Almost all patients in our study had at least pretreatment pelvic CT, allowing to detect any suspicious pelvic and/or paraaortic lymph nodes. Patients with radiologically suspicious lymph nodes had more frequent recurrences, mostly metastatic, and node positive disease was an important prognostic factor when it came to RFS. The presence of metastatic regional disease in cervical cancer correlates with a worse prognosis [21,22]. However, the 2009 FIGO classification was based purely on clinical examination and did not include lymph node assessment. The new 2018 FIGO classification [20] contains lymph node positive status (IIIC), which will stratify survival of cervical cancer patients more accurately.

Results from the Surveillance, Epidemiology, and End Results (SEER) database revealed a decline in the use of brachytherapy for cervical cancer between 1988 (83%) and 2009 (58%), while clearly demonstrating a benefit from BT-IC in terms of OS and RFS [9]. This trend is thought to be accompanied by an increase in the use of more conformal EBRT techniques in a boost delivery, such as intensity-modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT). Feasibility studies show that it is possible to adequately cover the target volume with SBRT while maintaining a similar dose distribution for critical organs [23]. However, questions remain about the radiobiological equivalency of both treatments, since brachytherapy is capable of delivering not only over 80 Gy EQD2 to the periphery of the tumor, but also doses over 120 Gy EQD2 to the central cervix [14]. Clinical results from SBRT boost are scarce and often contradictory. Using the National Cancer Database, Gill et al. reported inferior OS outcomes from IMRT and SBRT compared with BT-IC [10], while O'Donnell et al. described similar outcomes between SBRT and BT-IC [12].

The prospective multicenter EMBRACE study [24] demonstrated that the addition of MRI-guided adaptive brachytherapy according to GEC-ESTRO recommendations [25,26] resulted in improved local control, even in larger tumors, without additional toxicity. However, traditional brachytherapy applicators are sometimes still unhelpful in the treatment of cervical cancer patients, because of tumor size, lateralization, or technical inability to perform an intracavitary application. Interstitial brachytherapy techniques guided by ultrasound imaging, either alone [27] or combined with intracavitary applicators, could possibly allow for more patients to receive this highly needed boost to the tumor.

Conclusions

Brachytherapy boost provided better locoregional control and better survival outcomes compared with EBRT boost. Therefore, brachytherapy is an essential component in the treatment of cervical cancer patients and all efforts should be made to include this technique in the treatment plan.

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Disclosure

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