

Scientific Article

The Impact of High-Dose-Rate Brachytherapy: Measuring Clinical Outcomes in the Primary Treatment of Cervical Cancer



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Received 26 August 2019; revised 5 February 2020; accepted 8 February 2020

Abstract

Purpose: Radical concurrent chemoradiotherapy with combined external beam radiotherapy (EBRT) and brachytherapy is used to treat locally advanced cervical cancer. Our institution has transitioned to high-dose-rate (HDR) intracavitary brachytherapy (ICBT) from low-dose-rate (LDR) brachytherapy in 2008, and a review was conducted on the effect of this change on patient outcomes.

Methods and Materials: A single-arm retrospective chart review was performed on locally advanced (Fédération Internationale de Gynécologie et d'Obstétrique stage IB-IVA) patients with cervical cancer treated with combined external beam radiation therapy and HDR-ICBT with curative intent between 2008 and 2014. Clinical outcomes were evaluated, and multivariate analysis was performed to identify prognostic factors.

Results: Of the 76 patients selected, median age was 47.9 years and median follow-up was 5.2 years. Thirteen patients (17.1%) developed locoregional recurrence and 23 patients (30.3%) patients developed distant recurrence. Five-year progression-free survival and overall survival were 63.7% and 69.3%, respectively. A significant survival difference was found between stages ($P < .001$). Multivariate analysis found nodal involvement was strongly associated with poorer survival ($P = .007$).

Conclusions: Our experience with the transition to HDR-ICBT as part of concurrent chemoradiotherapy in treatment of locally advanced cervical cancer resulted in acceptable long-term outcomes and toxicity to that of LDR brachytherapy. Potential further improvement of treatment outcomes for patients may be possible with image guided brachytherapy and the addition of effective systemic therapy.

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Introduction

Cervical cancer is the third most common gynecologic malignancy worldwide with an annual incidence of more than half a million cases and 250,000 mortalities each year.¹ As are many types of cancers that are associated with viral infection, a higher incidence rate of such cancers is found in low- and middle-income countries,² largely owing to limited primary prevention practices, such as human papillomavirus vaccination,³ and secondary screening programs⁴ that are more easily accessible

Sources of support: None to declare.

Disclosures: None to declare.

Data availability: The data generated or analyzed during the current study are available from the corresponding author upon reasonable request.

Presented in abstract format at the European Society for Radiotherapy and Oncology on May 5-9, 2017, in Vienna, Austria; the Society of Gynecologic Oncology of Canada on June 22-24, 2017, in Ottawa, Canada; and the Canadian Association of Radiation Oncology on September 13-16, 2017, in Toronto, Canada.

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<https://doi.org/10.1016/j.adro.2020.02.003>

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in developed countries. However, even in developed countries, certain populations remain vulnerable to malignancy-associated infections with comparable mortality rate to that of developing countries, highlighting the importance of additional management in this population.⁵

Although surgery remains the standard of care for early-stage cervical cancer, several studies have demonstrated improved survival outcomes in patients treated with concurrent chemoradiotherapy for locally advanced disease (stage IB2-IVA). Concurrent chemoradiotherapy is now considered the standard of care for locally advanced cervical cancer.⁶⁻¹⁰ Intracavitary brachytherapy (ICBT) combined with external beam radiotherapy (EBRT) remains an essential part of definitive radiation treatment. Several modalities including low-dose-rate (LDR), pulsed-dose-rate (PDR), and high-dose-rate (HDR) brachytherapy have been developed. Although LDR brachytherapy has traditionally been used in the past, HDR-ICBT has gradually replaced LDR brachytherapy in the past decade owing to the many advantages of HDR-ICBT, including the availability of remote afterloading, thereby reducing radiation dose to medical personnel, shorter applicator treatment times (minutes vs days), and elimination of potential complications associated with prolonged immobilization from LDR brachytherapy, such as venous stasis, pulmonary embolus, patient discomfort, and longer hospital stays. Several studies have reported that the majority of centers worldwide have transitioned to exclusive HDR-ICBT from LDR brachytherapy by 2010.^{11,12} In Canada, this change was also accelerated by discontinuation of support for LDR applicators and afterloaders by a major commercial vendor by the end of 1999.¹³ Of note, a small subset of centers continue to practice PDR brachytherapy in many countries.¹⁴

We have published our previous experience with radical radiation therapy before¹⁵ and after¹⁶ the 1999 National Cancer Institute alert recommending the use of cisplatin-based chemoradiotherapy in the treatment of cervical cancer. This was followed by the transition to HDR-ICBT from LDR brachytherapy at our center in 2008. We herein present the result of the transition to HDR-ICBT and its effect on patient outcomes.

Methods

Institutional review board—approval was obtained before commencement of the study. A single-center retrospective chart review was conducted on consecutive locally advanced (stage IB-IVA, Fédération Internationale de Gynécologie et d'Obstétrique 2009 staging classification¹⁷) patients with cervical cancer treated with combined EBRT and HDR-ICBT between 2008 and 2014. Patients were treated with concomitant radical conformal radiation therapy and chemotherapy with HDR-ICBT

boost. All patients had been staged with both clinical examination and computed tomography (CT) scans of the abdomen and pelvis for local and regional disease and chest radiography for any suspicion of distant metastases. Magnetic resonance imaging (MRI) scans were used when available and have become a routine part of staging investigation after 2010. Positron emission tomography (PET)-CT scans were not routinely available for staging during the study period.

Patients were planned for EBRT to include the pelvis with or without para-aortic lymph node region, using intensity modulated radiation therapy or 4-field box type beam arrangement with 3-dimensional conformal techniques with dose prescription to the target volume using 6 to 18 megavoltage photons. EBRT was delivered at a median dose of 45 Gy in 25 fractions on weekdays and HDR-IBCT was delivered at a median dose 24 Gy in 3 weekly fractions to the prescription point. An intracavity ring and tandem applicator technique was used for the HDR-ICBT with remote afterloading using iridium-192 source. HDR-ICBT was initiated on the fourth or fifth week of pelvic EBRT. A Smit sleeve was often inserted for the first fraction under general anesthesia and subsequent HDR-ICBT was performed at weekly intervals usually under conscious sedation. No patient received EBRT on the same day as HDR-ICBT. Dose constraints (D_{2cc} , EQD2) include <90 Gy for urinary bladder and <75 Gy for rectum and sigmoid colon. Some patients (18.4%) received an EBRT boost (range, 300-1000 cGy) delivered simultaneously or sequentially to the primary or nodal disease if indicated. Systemic therapy consisted of weekly cisplatin (40 mg/m²) with a median of 5 cycles.

Orthogonal fluoroscopic imaging has been traditionally used for LDR brachytherapy at our institution with prescription dose to point A as per International Commission on Radiation Units and Measurements Report 38.¹⁸ After the transition to HDR-ICBT, the practice of using orthogonal fluoroscopic imaging and prescription dose to point A has been continued. After 2010, CT imaging was introduced for improved target and organs at risk (OAR) delineation, although the dose was still prescribed to point A. Image guidance technique for brachytherapy was not available at our institution during the study period owing to the lack of MRI-planning facilities. Therefore, it was not possible to routinely identify treatment targets.

Follow-up visits consisted of routine clinical examinations and imaging investigations with CT or MRI every 3 to 4 months in the first 2 years, followed by every 6 months for the subsequent 3 years. PET-CT was not part of routine follow-up investigations.

Statistical analysis was performed using IBM SPSS Statistics 25.0 (Aramonk, NY). Survival curves were generated with the Kaplan-Meier method. Log-rank test was used to calculate survival outcomes and compare the outcomes between stages. Multivariate Cox regression

Table 1 Patient demographics and tumor characteristics

Median age at diagnosis, y (range)	47.9 (24.3-89.3)
Median follow-up,* y (range)	5.2 (0.0-10.4)
Median tumor size, cm (range)	4.7 (1.2-9.5)
Histology, n (%)	
SCC	67 (88.2)
Adenocarcinoma	9 (11.8)
Grade, n (%)	
1	2 (2.6)
2	21 (27.6)
3	31 (40.8)
Unknown	22 (28.9)
Pelvic/para-aortic LN involvement, n (%)	
Yes	26 (34.2)
No	50 (65.8)
Fédération Internationale de Gynécologie et d'Obstétrique stage, n (%)	
I	12 (15.8)
II	28 (36.8)
III	33 (43.4)
IV	3 (3.9)

Abbreviations: LN = lymph node; SCC = squamous cell carcinoma.

* One patient recurred at distant site before end of treatment.

analysis was used to evaluate the associations between the following covariates with survival: size of tumor >5 cm, grade, histology, and nodal involvement of disease. Progression-free survival (PFS) was defined as the time interval between the end of radiation treatment and the date of locoregional or distant recurrence, disease progression, or death from any cause, whichever occurred first, and overall survival (OS) was defined as the time interval between the end of treatment and death from any cause. Marginal recurrence was defined as any recurrence where recurrent disease was within ≤2 cm of radiation therapy field edge or 50% prescription isodose, and distant recurrence was defined as any recurrence where recurrent disease was outside >2 cm of field edge or 50% prescription isodose.

Results

Patient demographics and tumor characteristics are summarized in Table 1. A total of 76 patients were identified and selected for final analysis. The median age at time of diagnosis was 47.9 years and median follow-up was 5.2 years. The majority of patients (55%) were postmenopausal at the time of diagnosis. The most common histology was squamous cell carcinoma (88.2%) followed by adenocarcinoma (11.8%). Median tumor size was 4.7 cm (range, 1.2-7.8 cm) based on CT imaging, and 34.2% of patients had radiologic evidence of nodal involvement of disease. All patients completed EBRT and HDR-ICBT as scheduled, and the median time interval between start and completion of radiation therapy was 50 days (range, 37-92 days). The majority of patients (97.4%) received chemotherapy in addition to radiation therapy, where 66% of patients completed all 5 planned cycles of chemotherapy and 82% of patients completed at least 4 cycles of chemotherapy (range, 1-6 cycles).

Clinical outcomes are summarized in Table 2. Among the entire cohort of 76 patients, a total of 13 patients (17.1%) had a component of locoregional recurrence and 23 patients (30.3%) patients had a distant recurrence. Nine patients (11.8%) had both locoregional and distant recurrence (Fig 1). Cumulative incidence rates of locoregional recurrence in stage I-IV were as follows: 0.0%, 14.3%, 24.2%, and 33.3%, respectively. Five-year locoregional failure-free survival across all stages was 81.5%. Median time to any recurrence from end of treatment was 7.2 months (range, 0.0-5.3 years), and one patient showed evidence of distant recurrence before the end of treatment. Median time to locoregional recurrence was 5.9 months (range, 0.0-2.7 years) and to distant recurrence was 8.0 months (range, 0.0-5.3 years). Among the 13 patients with locoregional recurrence, 5 patients (6.6%) had marginal recurrence. Three-year and 5-year PFS were 69.5% and 63.7%, respectively, and 3-year and 5-year OS were 70.8% and 69.3%, respectively (Fig 2).

Table 2 Survival outcomes according to stage

	Stage I (n = 12)	Stage II (n = 28)	Stage III (n = 33)	Stage IV (n = 3)	All patients (n = 76)
Locoregional recurrence, n (%) [*]	0 (0.0)	4 (14.3)	8 (24.2)	1 (33.3)	13 (17.1)
Distant recurrence, n (%) [*]	0 (0.0)	8 (28.6)	14 (42.4)	1 (33.3)	23 (30.3)
PFS (%)					
3 y	100.0	78.0	54.5	33.3	69.5
5 y	100.0	70.2	50.9	0.0	63.7
OS (%)					
3 y	100.0	78.0	57.6	33.3	70.8
5 y	100.0	74.1	57.6	0.0	69.3

Abbreviations: OS = overall survival; PFS = progression-free survival.

* Recurrence rates are based on cumulative incidence.

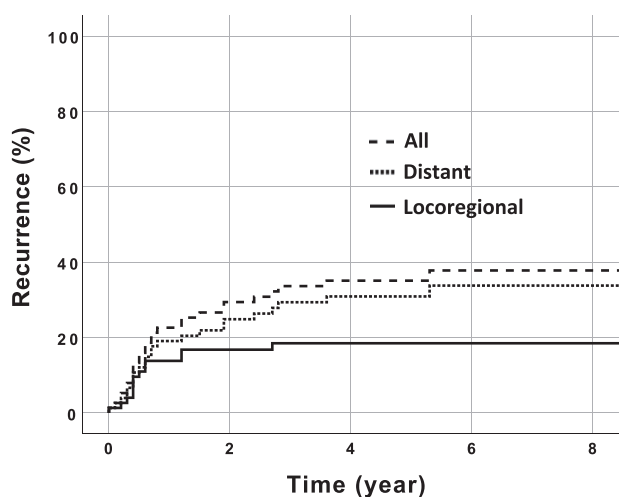


Figure 1 Cumulative incidence rates of locoregional, distant, and any recurrences.

Significant differences in PFS ($P < .001$) and OS ($P = .005$) were found between stages of disease (Fig 3). Multivariate analysis identified nodal involvement was strongly associated with PFS (HR 4.63; 95% confidence interval [CI], 1.51-14.1; $P = .007$), whereas histology ($P = .59$), tumor size >5 cm ($P = .96$), and grade ($P = .30$) were not associated with PFS or OS (Table 3). Documented grade ≥ 3 gastrointestinal and genitourinary toxicity was found in 16 patients (21.1%) and grade ≥ 3 hematologic toxicity seen in 26 patients (34.2%). There were no treatment-related deaths.

Discussion

Cervical cancer is highly curable with early stage disease, and the published literature demonstrates combining EBRT with brachytherapy can result in good

locoregional control even for locally advanced disease.¹⁹ The addition of weekly cisplatin-based chemotherapy further improves clinical outcomes.²⁰ The majority of experience at many centers has been focused on LDR-brachytherapy, although recent published literature has indicated HDR-brachytherapy could potentially result in comparable outcomes to LDR-brachytherapy.²¹⁻²⁴ There are no significant differences found in terms of overall survival, locoregional failure, or major complications between HDR and LDR brachytherapy, and this justifies the potential transition to an HDR-based practice in the radical management of cervical cancer.

Our institution has previously published results from a retrospective study in the LDR-brachytherapy era comparing radiation therapy with and without addition of chemotherapy in treatment of cervical cancer, where addition of chemotherapy was associated with significantly improved survival.¹⁶ Since the time of the publication of previous study in 2010, a transition has been made from LDR brachytherapy to HDR-ICBT in 2008 at our institution. In this retrospective study, we were able to demonstrate that despite the transition, not only was HDR-ICBT feasible in the current treatment for cervical cancer, but also HDR-ICBT appears to be associated with improved 5-year PFS, although the difference was seen across all stages of disease. One must note the survival improvement seen in this study cannot be solely attributed to the transition from LDR brachytherapy to HDR-ICBT, although many other potential factors may also have contributed to the differences observed between the 2 study periods, including improved target dose distribution, optimization of systemic therapy, better disease detection with higher sensitivity in more frequent use of MR scans, and better patient management overall. However, it is likely that the benefits of HDR-ICBT outweigh potential drawbacks compared with LDR brachytherapy, and the continuation of current practice of treatment for

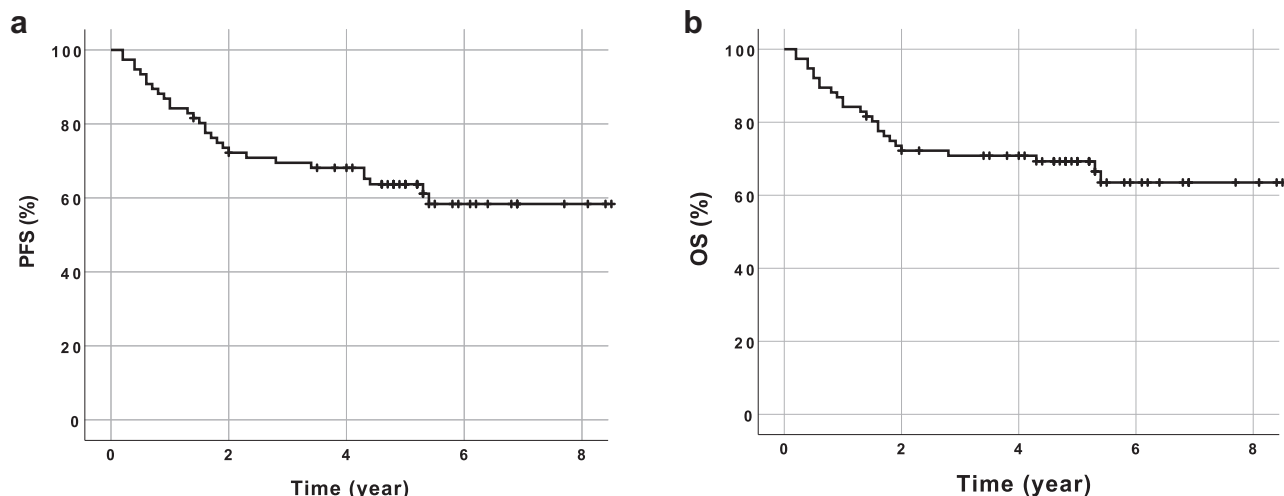


Figure 2 (a) Progression free survival (PFS) and (b) overall survival (OS) of all patients. Three-year and 5-year PFS were 69.5% and 63.7%, respectively, and 3-year and 5-year OS were 70.8% and 69.3%, respectively.

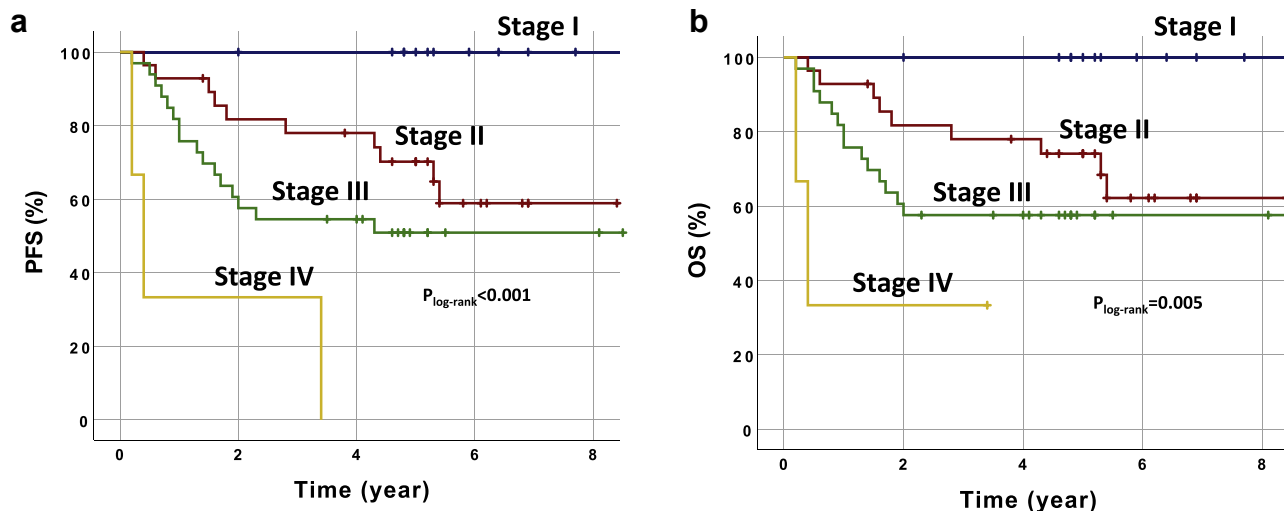


Figure 3 Comparison of (a) progression free survival (PFS) and (b) overall survival (OS) between stages of disease, according to 2009 Fédération Internationale de Gynécologie et d’Obstétrique staging classification. Significant differences in PFS ($P < .001$) and OS ($P = .005$) were found between the stages.

locally advanced cervical cancer using HDR-ICBT is justified.

At our institution, MR-guidance was introduced in 2015, and patients have been treated with HDR-ICBT with MR guidance since then. Such practice routinely includes contouring HR-CT and OAR structures in accordance with Image-guided intensity modulated External beam radiochemotherapy and MRI-based adaptive BRACHYtherapy in locally advanced Cervical cancer (EMBRACE)²⁵ recommendations, while prescribing dose to HR-CTV rather than to point A. This is consistent with the current standard of care for treatment of cervical cancer and may result in further improvements in patient outcomes, including better local disease control and potentially less treatment-related toxicity.

Multiple retrospective series have proposed combined use of image guidance, especially MR imaging, with ICBT²⁶⁻²⁹ or interstitial brachytherapy³⁰ for treatment of cervical cancer. D’Souza et al have described in their systematic review on image guided HDR-ICBT that CT

image guidance provides a more precise target volume delineation with higher conformal dose delivery than conventional 2-dimensional orthogonal radiography. Furthermore, compared with CT image guidance, MR image guidance is associated with greater accuracy in evaluating tumor infiltration into parametria and clearer soft tissue delineation between cervix, uterus and vagina.³¹ Similarly, at our institution, like many centers across the country, we are transitioning our practice into 3-dimension image-based brachytherapy from orthogonal imaging for treatment planning. This would potentially allow for better tumor delineation with dosimetric parameters as outlined in guidelines by The Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology working group.³² Such practice would especially be beneficial in the larger tumor cohort with potential parametrial tumor extension owing to the improved tumor delineation, visualization of applicator placement for a proper treatment planning, reduction in interobserver variation, potential dose

Table 3 Multivariate analysis for PFS and OS

Covariate	PFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Regional LN involvement*	4.63	1.51-14.1	.007	3.09	0.87-11.0	.082
Histology SCC	0.65	0.14-3.07	.59	1.10	0.12-8.12	1.00
Tumor size >5 cm	1.03	0.34-3.11	.96	1.03	0.30-3.57	.96
Grade	n/a	n/a	.30	n/a	n/a	.26
2	0.52	0.049-5.43	.58	0.27	0.58-1.28	.10
3	1.84	0.21-16.46	.59	3.66	0.78-17.24	.10

Abbreviations: CI = confidence interval; HR = hazard ratio; LN = lymph node; OS = overall survival; PFS = progression-free survival; SCC = squamous cell carcinoma.

* Regional LN involvement was associated with poorer PFS ($P = .007$).

escalation to the primary lesion, and dose reduction in adjacent OAR,^{33–38} which in turn could translate to the greater locoregional disease control and decrease in severe late complications.³⁹ Another possibility is adaptive dose escalation in the primary tumor based on response seen on MR images as highlighted by the data from the RetroEMBRACE study.⁴⁰

In their updated analysis, Tan et al describe the change in predominant relapse patterns from locoregional failure with conventional brachytherapy, to systemic failure after image guided brachytherapy, thus highlighting the excellent locoregional disease control with image guided brachytherapy and the transition of focus to more effective systemic therapy in the current era.⁴¹ This observation of distant recurrences predominating over locoregional relapses was also seen in our study. Another area of interest is the addition of PET-CT as part of initial staging investigation, where dose escalation in FDG-avid nodal areas could potentially result in greater regional disease control.⁴²

Lastly, despite the improved locoregional disease control with combined EBRT and HDR-ICBT in our study, distant relapse rate remains high (30.3% cumulative incidence rate). The high distant relapse rate calls for development of better systemic therapy as described earlier that could potentially translate into improved survival outcomes. A recent phase III clinical trial has demonstrated 3-year PFS improvement with the addition of adjuvant gemcitabine plus cisplatin to concurrent gemcitabine plus cisplatin and radiation in patients with stage IIB-IVA cervical cancer.^{43,44} The phase III clinical trial (Outback ANZGOG0902/GOG0274/RTOG1174) is ongoing and it is investigating the potential benefit of adjuvant carboplatin plus paclitaxel to cisplatin-based chemoradiotherapy in stage IB-IV cervical cancer.⁴⁵

Strengths of our study include the homogeneous patient population in a single institution with minimal variation in treatment practice among physicians. In addition, the long median follow-up period of 5.2 years in our study would capture the majority of events, although most of recurrences occurred within 2 years. Limitations of the study include retrospective nature with potential bias and a small population size, limiting the significance of the results from the study.

Conclusions

Locoregional disease control for cervical cancer remains excellent when EBRT is combined with HDR-ICBT and concurrent chemotherapy, especially for stage IB disease. The findings are comparable to that of LDR brachytherapy from previous practices at our institution. There is room for potential improvement in terms of locoregional control with more precise target dose delivery with incorporation of MR-guided brachytherapy.

Distant relapses remain as a challenging problem and further studies evaluating effective systemic treatments are needed to reduce distant relapses and increase survival.

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