Implementation of image-guided brachytherapy (IGBT) for patients with uterine cervix cancer: a tumor volume kinetics approach

Heloisa de Andrade Carvalho, MD, PhD1, Lucas Castro Mendez, MD1, Silvia Rachwanski Stuart, MD1, Roger Guilherme Rodrigues Guimarães, MD1, Clarissa Cerchi Angotti Ramos, MD1, Lucas Assad de Paula, MD2, Camila Pessoa de Sales, PhD1, André Tsun Chih Chen, MD1, Roberto Blasbalg, MD, PhD2, Ronaldo Hueil Baroni, MD, PhD2

1Radiotherapy Division, 2Magnetic Resonance Division, Departamento de Radiologia e Oncologia Faculdade de Medicina da Universidade de São Paulo, Brazil

Abstract

**Purpose:** To evaluate tumor shrinking kinetics in order to implement image-guided brachytherapy (IGBT) for the treatment of patients with cervix cancer.

**Material and methods:** This study has prospectively evaluated tumor shrinking kinetics of thirteen patients with uterine cervix cancer treated with combined chemoradiation. Four high dose rate brachytherapy fractions were delivered during the course of pelvic external beam radiation therapy (EBRT). Magnetic resonance imaging (MRI) exams were acquired at diagnosis (D), first (B1), and third (B3) brachytherapy fractions. Target volumes (GTV and HR-CTV) were calculated by both the ellipsoid formula (VE) and MRI contouring (VC), which were defined by a consensus between at least two radiation oncologists and a pelvic expert radiologist.

**Results:** Most enrolled patients had squamous cell carcinoma and FIGO stage IIB disease, and initiated brachytherapy after the third week of pelvic external beam radiation. Gross tumor volume volume reduction from diagnostic MRI to B1 represented 61.9% and 75.2% of the initial volume, when measured by VE and VC, respectively. Only a modest volume reduction (15-20%) was observed from B1 to B3.

**Conclusions:** The most expressive tumor shrinking occurred in the first three weeks of oncological treatment and was in accordance with gynecological examination. These findings may help in IGBT implementation.

Key words: brachytherapy, cervical cancer, cervix cancer, MRI.

Purpose

Uterine cervix cancer has a high incidence in developing countries and, despite the screening programs, diagnosis in an advanced stage is still common. In Latin America, incidence rates range from 20 to 80 per 100 000 women per year [1], however, screening programs are not available for all women, resulting in a small impact effect in mortality reduction. In Brazil, the National Cancer Institute estimates an incidence of 16,340 new cervix cancer cases in 2016 with an estimated risk of 15.85/100 000 women [2]. Fortunately, both prophylaxis and management of patients with uterine cervix cancer have improved in recent years. This evolution has been mostly triggered by the new development of targeted systemic therapies and by advances in tridimensional (3D) brachytherapy.

Compatible computed tomography (CT) and magnetic resonance (MRI) tandem, ring, and ovoids have enabled the acquisition of 3D pelvic images with the applicators placed in the treatment position, allowing a good perception of tumor volume and its relation to the applicators. To help clinicians move forward and standardize treatments in this new technique, guidelines in image-guided brachytherapy (IGBT) have been written [3]. It was demonstrated that tumor coverage with the conventional two-dimensional (2D) plan, based on semi-orthogonal radiographs, was suboptimal, especially for large lesions, and IGBT could achieve a better tumor coverage and reduce dose to normal tissue [4]. In fact, great outcomes were reported by the Vienna and Aarhus groups [5,6,7], suggesting the superiority of IGBT against conventional brachytherapy. Better toxicity profile, higher local control, and specific disease-free survival were also observed in these reports. Public health in developing countries has limited resources, and implementation of a new technology should be rationalized and confronted with its related...
costs. Despite the benefits associated with IGBT in cervix carcinoma treatment, MRI availability and costs in each fraction of brachytherapy plus staff time consumed to perform the treatment represent some of the limiting factors. Thus, there is a need for further progress with regards to patient stratification and procedure evaluation to leverage a more positive cost-effective ratio. In this scenario, the Vienna group \cite{5,6} has reported that patients who benefit the most from IGBT are those with locally advanced disease, particularly women with tumors larger than 5 cm.

In 2010, our institution started a study for implementation of 3D IGBT. One of the goals was to optimize the resources for the procedure. In preparation to start an IGBT program, a tumor volume regression evaluation was done. This study aimed to evaluate tumor regression kinetics pattern in patients with cervical cancer treated with chemoradiation.

Material and methods

This study was approved by the institutional ethical committee (Comissão de Ética para Análise de Projetos de Pesquisa – CAPPesq da Diretoria Clínica do HCFMUSP) and registered as: CAPPesq no 1100/08. Before the beginning of the study, all patients had signed an informed consent.

From February 2010 to December 2011, fourteen patients with confirmed histological diagnosis of cervix squamous cell or adenocarcinoma were enrolled. Good performance status (ECOG < 3), a pelvic MRI at diagnosis, and FIGO stages IB to IIIB were required for inclusion in this study.

Patients were recruited sequentially and treated in accordance to the institutional protocol, which comprises additional local staging with pelvic MRI, pelvic external beam radiation therapy (EBRT) with concomitant weekly cisplatin-based chemotherapy, and two-dimensional (2D) intracavitary high-dose-rate brachytherapy (HDRB). Pelvic EBRT was performed with 6 or 15 MV photons, in 25 fractions of 1.8 Gy each (45 Gy total dose) with a 4-field conformal box technique. Patients with involved parametria received a 14 Gy boost in 7 fractions with opposed anterior-posterior/posterior-anterior fields and central shielding. High-dose-rate brachytherapy was delivered during EBRT once a week in four fractions of 7 or 7.5 Gy, prescribed at Manchester point A (7.5 Gy was prescribed for stage III patients). Dose constraints at ICRU 38 bladder and rectal points were limited to 65% of point A dose. In our practice, patients are routinely reassessed with gynecological exams after the second week of EBRT in order to evaluate local anatomy/geometry for brachytherapy. If brachytherapy is not performed, patients continue through weekly gynecological exams until proper geometry is achieved. Usually, these patients start brachytherapy after the end of the pelvic irradiation, and fractions are delivered twice a week in order to finish the whole treatment in less than 8 weeks. Chemotherapy consisted of weekly cisplatin 40 mg/m² up to six cycles given concomitantly to radiotherapy. No chemotherapy or EBRT were allowed on the days of brachytherapy.

The brachytherapy protocol for implementation of 3D IGBT followed exactly the same schedule, except for the performance of MRI in the first and third HDRB fractions, and CT scans in the second and fourth HDRB fractions. Local anesthesia and conscious sedation were used for cervix dilation and placement of the CT-MR compatible tandem-ring applicator (Nucletron®, an Elekta Company, Sweden), under ultrasound guidance. All patients were treated with standard 2D technique using semi-orthogonal pelvic radiographs. Plato® version 14.1 and subsequently Oncentra Masterplan® version 4.1 (Nucletron®, an Elekta Company, Sweden) were the planning systems used for calculations. Magnetic resonance images, both at diagnosis and at brachytherapy, were performed with a 1.5 Tesla GE Signa HDxt scanner (GE Healthcare, Chalfont St. Giles, UK [a unit of General Electric Company])

Results

Patients characteristics

One out of fourteen patients enrolled in this protocol was excluded due to psychiatric disorder, which disabled MRI to be performed during brachytherapy.
Thus, thirteen women with 39 MRIs were the object of this study. Patients median age was 46 years (range 31 to 76 years) and all of them had ECOG performance status equal to zero. Nine patients had squamous cell histology and the others adenocarcinoma. Two patients presented FIGO stage IB, one stage IIA, nine were IIB, and one IIIB. Among IIB cases, two presented with enlarged pelvic lymph node considered to be positive.

Treatment

Radiotherapy started with a median delay of 49 days (range 10 to 102 days) from the date of diagnostic pelvic MRI, and the median start time between EBRT and the first brachytherapy fraction was 36 days (range 23 to 95 days). All patients received six cycles of cisplatin, except for one, who received five cycles. The entire oncological treatment was completed within a median time of 60 days (range: 47 to 83 days). Three patients presented more extended total treatment time mainly due to interruptions related to hematological toxicity of the chemoradiation schedule. Seven patients initiated HDRB between the third and fifth week of EBRT and six after 45 Gy EBRT to the pelvis.

All HDRB fractions were performed with tandem and ring applicator using the rectal retractor. One out of 13 patients had the ring diameter reduced from 34 mm to 30 mm along treatment; two patients had the tandem length shortened from 60 mm to 40 mm, and in one patient, a different applicator angle was used along brachytherapy fractions.

Volumes analysis

Figure 1 shows tumor volume regression throughout oncological treatment. Most of the gross tumor volume reduction occurred from the diagnostic MRI to the first brachytherapy fraction (Figure 2).

Tables 1 and 2 compare tumor volumes estimated by the ellipsoid formula (VE) and calculated by MRI contouring (VC) in three different moments: D, B1, and B3. A mean absolute volume reduction of approximately 16 cc was observed between diagnosis and the first brachytherapy fraction by both calculation methods. This volume reduction represented 61.9% and 75.2% of the diagnostic GTV, when measured by VE and VC, respectively. We compared tumor kinetics of the seven patients in whom brachytherapy was started before the end of EBRT with the other six where HDRB started after completion of EBRT (45 Gy). VE and VC at diagnosis were similar in both groups (p = 0.173 and 0.686, respectively), as the
tumor regression pattern evaluated by VE and VC at B1 ($p = 0.116$ and 0.753, respectively).

Mean overall tumor shrinkage, evaluated by VE and VC, from the diagnostic MRI to third brachytherapy fraction was 82.7% and 89.0%, respectively. Thus, only a modest reduction of 15-20% of the GTV volume was seen between the first and third HDRB fractions. Again, no statistically significant differences were observed in tumor kinetics when patients were evaluated according to the dose of EBRT received at B3.

No significant correlation was found between VE and VC at the diagnostic MRI. VE calculation overestimated the contoured volume. However, VE and VC were statistically correlated in both B1 and B3, with a higher correlation index observed in smaller tumor volumes (Figure 3, Table 3).

High-risk clinical target volume in B1 and B3 were also evaluated. VC presented similar volumes in B1 and B3, with a median volume estimated as 21.4 cc (7-151 cc) and 21.6 cc (11-97 cc), respectively. Both volumes were highly correlated ($\rho = 0.891/ \ p = 0.001$; Spearman correlation test).

**Discussion**

Brachytherapy is fundamental in the treatment of advanced uterine cervix cancer because improves overall survival [10]. Image-guided brachytherapy is a recent evolution from 2D brachytherapy and allows clinicians to optimize treatment to a visible and measurable gross tumor volume. This is particularly useful when we are faced with large tumors, as often diagnosed in developing countries [11]. Thus, dose prescription and isodose

---

**Table 1.** Ellipsoid formula (VE) estimated volume along treatment: at diagnosis (GTV$_D$), first (GTV$_{B1}$), and third (GTV$_{B3}$) brachytherapy fractions

| Volume | Median (IQR) (cc) | Shrinkage (%) | $p^*$ | $p^#$ |
|--------|------------------|--------------|-------|-------|
| GTVD   | 25.5 (17.4-116.8)| 61.9         | 0.001 | 0.0001|
| GTVB1  | 9.7 (1.3-18.0)   | 54.7         | 0.008 |       |
| GTVB3  | 9.7 (1.3-18.0)   | 82.7         | 0.005 |       |
| GTVD   | 25.5 (17.4-116.8)|             |       |       |
| GTVB1  | 4.4 (0.05-16.6)  |             |       |       |

$^*$ Wilcoxon signed rank test, $^#$ Friedman test

**Table 2.** Slice-by-slice delineation volume (VC) along treatment: at diagnosis (GTV$_D$), first (GTV$_{B1}$), and third (GTV$_{B3}$) brachytherapy fractions

| Volume | Median (IQR) (cc) | Shrinkage (%) | $p^*$ | $p^#$ |
|--------|------------------|--------------|-------|-------|
| GTVD   | 21.0 (11.3-103.9)| 75.2         | 0.001 | 0.0001|
| GTVB1  | 5.2 (0.5-18.9)   | 55.8         | 0.008 |       |
| GTVB3  | 2.3 (0-14.5)     | 89.0         | 0.005 |       |

$^*$ Wilcoxon signed rank test, $^#$ Spearman’s correlation test

**Table 3.** Tumor volumes comparisons calculated by VE and VC at diagnosis (GTV$_D$), first (GTV$_{B1}$), and third (GTV$_{B3}$) brachytherapy fractions

| Volume | Median (IQR) (cc) | Range (cc) | $p^*$ | $\rho^*$ | $p^#$ |
|--------|------------------|------------|-------|---------|-------|
| GTVD   | VE 25.5 (17.4-116.8)| 12.6-184.2 | 0.023 | 0.505   | 0.078 |
|        | VC 21.0 (11.3-103.9)| 7.6-164.8  |       |         |       |
| GTVB1  | VE 9.7 (1.3-18.0)  | 0.5-86.3   | 0.650 | 0.604   | 0.029 |
|        | VC 5.2 (0.5-18.9)  | 0.0-151.5  |       |         |       |
| GTVB3  | VE 4.4 (0.05-16.6) | 0.0-38.2   | 0.678 | 0.726   | 0.017 |
|        | VC 2.3 (0-14.5)    | 0-97.7     |       |         |       |

$^*$ Wilcoxon signed rank test, $^*$ Spearman’s correlation test

IQ = interquartile range, VE = ellipsoid formula, VC = slice-by-slice delineation volume

---

![Fig. 3. Tumor median volumes calculated by ellipsoid formula (VE) and slice-by-slice delineation (VC) at magnetic resonance imaging diagnosis (D), first (B1), and third (B3) brachytherapy fractions.](image-url)
shaping can be individualized in accordance to specific tumor, the cervix and suspicious extra-cervical residual tissues while taking the initial tumor shape and size into account, and OAR anatomy. As expected, toxicity profile related to this technique is milder in comparison to that achieved with 2D brachytherapy [12,13,14]. Moreover, absolute local control can be approximately 20% higher than published results using 2D technique in the literature resulting in an absolute 3-year cancer specific survival benefit of 13 to 30% in patients with tumors larger than 5 cm [6,12,13].

In order to perform IGBT, a 3D pelvic image acquisition with the applicators in place is necessary. Both CT and MRI are useful in this setting but MRI provides a better soft tissue contrast and is superior in gross tumor volume definition [15,16]. However, MRI is more expensive than CT and its image acquisition is longer, thus limiting its use in developing countries where cervix cancer has a high incidence.

In the present study, tumor kinetics’ along cancer treatment was evaluated by serial MRIs. Around 70% tumor volume reduction was achieved from diagnosis to the first HDRB fraction, which is in accordance to others findings [17]. Considering that in the present patient cohort there was a median delay of 49 days from the diagnostic MRI to the initiation of brachytherapy, it is possible that the relative volume reduction between tumor volume prior to EBRT and the first fraction of brachytherapy would be even larger than 70%. This delay may represent a limitation of our study. Nevertheless, this important volume reduction in the first weeks of EBRT suggests that IGBT could start, at least after the third week of EBRT, since after this period, a substantial regression of tumor’s volume is not expected. One may argue that a maximum tumor regression is observed at the end of EBRT, and thus, IGBT should be performed at this point, making our analysis irrelevant. However, in this scenario, brachytherapy would preferably be delivered in two fractions per week in order to avoid an extended total treatment time over 56 days. This may represent a burden in very busy departments like ours, justifying why efforts are done to optimize MRI to treatment also represent limitations of this study. On the other hand, our results may better reflect obstacles and difficulties to implement the technology at our institution, in a group of patients treated according to our daily routine. But, even with these limitations, our results were in agreement with others that looked at tumor shrinkage during irradiation [17,20,21]. In these studies, the effects of EBRT alone or brachytherapy on tumor shrinkage were evaluated. In our study, tumor regression was evaluated in a different treatment schedule with HDRB performed during chemoradiation. Brachytherapy when performed during chemoradiation may present an even higher tumor regression and the influence of this combination may be explored in further studies.

The main objective of this study was the evaluation of the tumor shrinkage during treatment. In addition, the feasibility of the procedure was evaluated for further implementation of the method in the institution. No sample size was calculated upfront, neither a maximum time between the diagnosis MRI and the initiation of EBRT or HDRB was required. We are aware that the small number of patients and the variation of time elapsed since diagnosis MRI to treatment also represent limitations of this study. On the other hand, our results may better reflect obstacles and difficulties to implement the technology at our institution, in a group of patients treated according to our daily routine. But, even with these limitations, our results were in agreement with others that looked at tumor shrinkage during irradiation [17,20,21]. In these studies, the effects of EBRT alone or brachytherapy on tumor shrinkage were evaluated. In our study, tumor regression was evaluated in a different treatment schedule with HDRB performed during chemoradiation. Brachytherapy when performed during chemoradiation may present an even higher tumor regression and the influence of this combination may be explored in further studies.

A parallel result of this study was the comparison between the different methods of volume evaluation throughout treatment. Not surprisingly, the ellipsoid formula overestimated the gross tumor volume on the staging MRI. As expected, large tumor volumes with irregular shapes are not well estimated by VE that takes into consideration spheroid shapes using only three planes coordinates. As tumor shrinks, the estimated VE better correlates with VC. These findings are in accordance with Mayr et al. [9], and may indicate that the results of Dimopoulos et al. [17], based on the ellipsoid formula, may either under or overestimate tumor regression. Despite these differences between tumor volumes measured by
VE and VC due to limitations of the ellipsoid formula, both methods were consistent and presented a similar pattern of tumor volume reduction along treatment as shown in Figure 2. In addition, the volumes were defined by a consensus of at least three experienced professionals among radiologists and radiation oncologists, which gives reliability to the measures performed, and prevents delineation uncertainties [22]. These findings should be validated with a larger number of patients.

Not in the scope of this study but worth to comment, tumor regression during treatment may also be used as a prognostic factor [9,23,24,25], and as a very useful tool in order to pre-plan the brachytherapy procedure – intracavitary only or associated with interstitial implant [26].

The level of MRI utilization in IGBT depends on the infrastructural capabilities of individual centers, ranging from no use at all to repetitive imaging during EBRT and each IGBT fraction [27]. Despite the large number of uterine cervix cancer cases at our institution, only two patients per month could be recruited due to the overloading of the MRI agenda, which reflects the difficulties faced by our country, even in a reference center. For this same reason, studies looking at resource’s optimization are warranted and welcome in this context.

The benefits of the better use of technical resources come with the charge of personnel training and the more time-consuming of the whole treatment process. The later represents a limitation for the routine use of 3D IGBT in cervix cancer: report on the Vienna University Hospital experience. Most expressive tumor shrinkage occurs during the first three weeks of chemoradiation. Clinical evaluation by gynecological exams helped to determine the optimal time for brachytherapy and were in accordance with imaging exams. This finding may help in the decision making process of 3D-IGBT implementation.

Conclusions

Most expressive tumor shrinkage occurs during the first three weeks of chemoradiation. Clinical evaluation by gynecological exams helped to determine the optimal time for brachytherapy and were in accordance with imaging exams. This finding may help in the decision making process of 3D-IGBT implementation.

Disclosure

Authors report no conflict of interest.

References

1. Villa L. Cervix cancer in Latin America and the Caribbean: the problem and the way to solutions. Cancer Epidemiol Biomarkers Prev 2012; 21: 1409-1413.
2. Brasil, Ministério da Saúde, INCA. Estimativa 2016: incidência de câncer no Brasil; Instituto Nacional de Câncer José Alencar Gomes da Silva – Rio de Janeiro: INCA, 2015. Available at: www.inca.gov.br
3. Haie-Meder C, Pötter R, Van Limbergen E et al. Recommendations from Gynecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 2005; 74: 235-245.
4. Zwahlen D, Jezioranski K, Chan P et al. Magnetic resonance imaging-guided intracavitary brachytherapy for cancer of the cervix. Int J Radiat Oncol Biol Phys 2009; 74: 1157-1164.
5. Pötter R, Dimopoulos J, Georg P et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. Radiother Oncol 2007; 83: 148-155.
6. Pötter R, Georg P, Dimopoulos JC et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervix cancer. Radiother Oncol 2011; 100: 116-123.
7. Lindegaard JC, Fokdal LU, Nielsen SK et al. MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective. Acta Oncol 2013; 52: 1510-1519.
8. Dimopoulos JC, Petrow P, Tanderup K et al. Recommendations from Gynecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MRI imaging within the frame of image based adaptive cervix cancer brachytherapy. Radiother Oncol 2012; 103: 113-122.
9. Mayr NA, Taoka T, Yuh WT et al. Method and timing of tumor volume measurement for outcome prediction in cervical cancer using magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2002; 52: 14-22.
10. Han K, Milosevic M, Fyles A et al. Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys 2013; 87: 111-119.
11. Thuler LCS, de Aguiar SS, Bergmann A. Determinantes do diagnóstico em estádio avançado do câncer do colo do útero no Brasil. Rev Bras Ginecol Obstet 2014; 36: 237-243 [Article in Portuguese].
12. Pötter R, Knoche TH, Fellner C et al. Definitive radiotherapy based on HDR brachytherapy with iodium 192 in uterine cervix carcinoma: report on the Vienna University Hospital findings (1993–1997) compared to the preceding period in the context of ICRU 38 recommendations. Cancer Radiother 2000; 4: 159-172.
13. Tan LT, Coles CE, Hart C et al. Clinical impact of computed tomography-based image-guided brachytherapy for cervix cancer using the tandem-ring applicator – the Addenbrooke’s experience. Clin Oncol (R Coll Radiol) 2009; 21: 175-182.
14. Kang HC, Shin KH, Park SY et al. 3D CT-based high-dose rate brachytherapy for cervical cancer: clinical impact on late rectal bleeding and local control. Radiother Oncol 2010; 97: 507-513.
15. Beriwal S, Kannan N, Kim H et al. Three-dimensional high dose rate intracavitary image-guided brachytherapy for the treatment of cervix cancer using a hybrid magnetic resonance imaging/computed tomography approach: feasibility and early results. Clin Oncol (R Coll Radiol) 2011; 23: 685-690.
16. Dimopoulos JC, Schard G, Berger D et al. Systematic evaluation of MRI findings in different stages of treatment of cervix
cancer: potential of MRI on delineation of target, pathoanatomic structures, and organs at risk. *Int J Radiat Oncol Biol Phys* 2006; 64: 1383-1388.

17. Dimopoulos JC, Schir G, Baldinger A et al. MRI assessment of cervical cancer for adaptive radiotherapy. *Strahlenther Onkol* 2009; 185: 282-287.

18. Owrangi AM, Prisciandaro JJ, Soliman A et al. Magnetic resonance imaging-guided brachytherapy for cervical cancer: initiating a program. *J Contemp Brachytherapy* 2015; 7: 417-422.

19. Nesvacil N, Pöttler R, Sturdza A et al. Adaptive image guided brachytherapy for cervical cancer: a combined MR/CT-planning technique with MRI only at first fraction. *Radiother Oncol* 2013; 107: 75-81.

20. Mayr NA, Magnotta VA, Ehrhardt JC et al. Usefulness of tumor volumetry by magnetic resonance imaging in assessing response to radiation therapy in carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1996; 35: 915-924.

21. Hatano K, Sekiya Y, Araki H et al. Evaluation of the therapeutic effect of radiotherapy on cervical cancer using magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 1999; 45: 639-644.

22. Petrič P, Hudej R, Rogelj P et al. Uncertainties of target volume delineation in MRI guided adaptive brachytherapy of cervix cancer: a multi-institutional study. *Radiother Oncol* 2013; 107: 6-12.

23. Mayr NA, Yuh WT, Taoka T et al. Serial therapy-induced changes in tumor shape in cervical cancer and their impact on assessing tumor volume and treatment response. *AJR Am J Roentgenol* 2006; 187: 65-72.

24. Mayr NA, Wang JZ, Lo SS et al. Translating response during therapy into ultimate treatment outcome: a personalized 4-dimensional MRI tumor volumetric regression approach in cervical cancer. *Int J Radiat Oncol Biol Phys* 2010; 76: 719-727.

25. Wang JZ, Mayr NA, Zhang D et al. Sequential magnetic resonance imaging of cervical cancer: the predictive value of absolute tumor volume and regression ratio measured before, during, and after radiation therapy. *Cancer* 2010; 116: 5093-5101.

26. Fokdal L, Tanderup K, Hokland SB et al. Clinical feasibility of combined intracavitary/interstitial brachytherapy in locally advanced cervical cancer employing MRI with a tandem/ring applicator in situ and virtual preplanning of the interstitial component. *Radiother Oncol* 2013; 107: 63-68.

27. Petrič P, Mohammed-Al-Hammadi N. MRI findings at image guided adaptive cervix cancer brachytherapy: radiation oncologist’s perspective. *J Contemp Brachytherapy* 2014; 6: 215-222.

28. Moraes FY, Marta GN, Hanna SA et al. Around the globe: Brazil’s challenges and opportunities. *Int J Radiat Oncol Biol Phys* 2015; 92: 707-712.