Original paper

Initial experience using superflab as intravaginal packing during interstitial brachytherapy for advanced gynecologic cancer

Michael Kharouta, MD, Martha Malin, PhD, Christina Son, MD, Hania Al-Hallaq, PhD, Yasmin Hasan, MD

Department of Radiation and Cellular Oncology, University of Chicago Medical Center, Chicago, USA

Abstract

Purpose: Interstitial brachytherapy implemented for locally advanced gynecologic cancer can result in toxicity due to the proximity of organs at risk (OAR). We report our experience using superflab bolus as vaginal packing to displace OAR during interstitial brachytherapy.

Material and methods: Twelve patients with stage IB-IVA gynecologic cancer were treated with definitive chemoradiation including interstitial brachytherapy. A Syed template was used for a computed tomography (CT)-based pre-plan with magnetic resonance imaging (MRI) fusion. A 1-2 cm superflab bolus was cut and sterilized. The tandem and obturator were placed, and superflab was then inserted into the vagina. Interstitial needles were then placed through the template and superflab as per the pre-plan under transabdominal ultrasound guidance. Prescription doses ranged from 85-90 Gy EQD_2 including external beam radiation therapy (EBRT). 5-6 Gy per fraction was delivered biologically effective dose (BID) over 2-3 days in 1-2 implants. Toxicities were evaluated post-treatment, 1 month, and 3 months.

Results: The rectum, bladder, and sigmoid had significant average displacement from the prescription isodose line. The average reduction in D_{2cc} between pre- and post-implant was 5.19 Gy per fraction ($p < 0.0001$), 7.19 Gy ($p < 0.0004$), and 1.78 Gy ($p < 0.003$) for the rectum, bladder, and sigmoid, respectively. The high-risk target volume (HR-TV) received a median D_{90} of 104% (range, 58-122%) of the prescription dose, and 92% (range, 71-131%) in the pre-/post-implant plans, respectively ($p = 0.4$).

Conclusions: Our initial experience with superflab as vaginal packing demonstrates technical feasibility and dosimetric improvement for OAR.

J Contemp Brachytherapy 2018; 10, 3: 218–224
DOI: https://doi.org/10.5114/jcb.2018.76522

Key words: brachytherapy, interstitial, intravaginal, radiotherapy, superflab.

Purpose

The goal of brachytherapy treatment for gynecologic cancers is to maximize the therapeutic ratio. Recent trials emphasize the importance of reducing radiotherapy doses to organs at risk (OAR) [1,2,3]. Clinical trials such as EMBRACE II recommend even further dose reductions to OAR and increased dose to the target to improve patient outcomes [4]. These metrics may be achieved with magnetic resonance imaging (MRI) guidance, however alternative methods of normal tissue sparing warrant exploration considering these more recent planning goals.

Mechanical displacement of OAR is an effective method for reducing dose to the bladder and rectum in brachytherapy [5,6,7]. This follows from the inverse square law; the relative dose rate from a point source decreases exponentially with the distance from the source [8]. This is a critical element of both low-dose-rate (LDR) and high-dose-rate (HDR) brachytherapy. While brachytherapy allows for reduction of incident radiation passing through normal structures by placing the source close to the target, nearby OAR are exposed to high per-fraction doses, which can result in greater toxicity. Methods for displacement of OAR have included rectal retractors, vaginal gauze packing, and intravaginal balloons [5,6,7,9]. Each of these has specific advantages with regard to ease and consistency of deployment, cost, and dose reduction to nearby organs.

Interstitial brachytherapy is a technique commonly used for advanced gynecologic cancer when geometric parameters prevent adequate coverage of the target with other methods such as tandem and ovoids or ring applicators. When using a template-based interstitial approach, the insertion of packing material may be difficult due to the template blocking of packing material placement. Traditional packing methods such as vaginal gauze packing or the use of balloons can be challenging to implement, as the path of the catheters often traverses the space occupied by the packing material. The increased technical difficulty of these packing methods may lead to

Address for correspondence: Yasmin Hasan, MD, Department of Radiation and Cellular Oncology, University of Chicago Medical Center, USA, The University of Chicago Medicine, 5841 S. Maryland Avenue, MC 9006 Chicago, IL 60637, USA, phone: + 1 773 702-0817, fax: +1 773 834-7340, e-mail: yhasan@radonc.uchicago.edu

Received: 20.12.2017
Accepted: 04.05.2018
Published: 30.06.2018

increased OAR dose and associated toxicity. The rates of rectal, sigmoid, and genitourinary toxicity reported with interstitial brachytherapy for gynecological cancers range from 5-28% at 2 years post-treatment [10,11,12,13]. To our knowledge, there are no published reports describing routine use of packing for interstitial brachytherapy. Additionally, data on gauze packing in intracavitary (i.e. tandem and ovoids or ring applicator) brachytherapy seem to indicate that packing variability and inadequate packing technique can lead to a decrease in disease-free survival in patients receiving HDR brachytherapy [14].

In light of the limited data and clinical experience describing the use of packing for interstitial brachytherapy for gynecologic cancer, we explored using bolus material as intravaginal packing during interstitial cases for patients with bulky or residual disease after receiving external beam radiation therapy (EBRT) for locally advanced or recurrent gynecologic cancers. Superflab bolus is a standardized, homogenous substance made of vinyl plastic that is commonly used to provide a tissue-equivalent dose buildup layer. It is flexible, latex free, conformal to the contours of a patient's anatomy, and resistant to drying or swelling with changes in ambient moisture [15]. It can be cleaned, cut to a desired shape, and catheters may be passed through it with minimal force or damage to its structure.

Table 1. Patient characteristics

Patients (*n*)	12
Age (years)	
Median	54.5
Range	37-75
Tumor grade (*n*)	
1	3
2	4
3	2
Unknown	3
FIGO stage (*n*)	
I	2
II	2
III	5
IV	3
Tumor maximum dimension (cm)	
Median	4.95
Range	3.5-9.9
Lymphatic or vascular space invasion (*n*)	
Present	42
Not Present	33
Unknown	25

The aim of this study is to report our initial clinical experience using custom-cut, 1-2-centimeter-thick superflab bolus as vaginal packing material for interstitial brachytherapy. Our goal is to establish the feasibility of the use of superflab in this setting, describe the technical details of its use, and characterize the OAR displacement and dosimetric benefit to OAR in a series of patients with locally advanced cervical cancer.

Material and methods

Patient characteristics and treatment

From June 2015 to August 2016, 12 patients ages 39-76 years (median, 55 years) with stage IB-IVA locally advanced and recurrent gynecologic cancer were treated with definitive concurrent chemoradiation including interstitial brachytherapy (16 total implants) at a single institution. Patient characteristics are displayed in Table 1. A Syed interstitial template was used for a computed tomography (CT)-based pre-plan with MRI fusion and for each implant in 10/12 patients, and with CT alone in 2/12 patients; 4/12 patients had the MRI performed with the applicator and template in place. No catheters were placed for the pre-plan.

The interstitial procedures were performed using transabdominal ultrasound (US) guidance with bladder filling. A 1-2 cm superflab bolus by Radiation Products Design (RPD) was cut into 1-2 approximately 1 × 3 inch strips and soaked in betadine solution in the procedure room. After the tandem and obturator were placed in the uterus and vagina, respectively, the bolus material was manually inserted longitudinally into the vagina just posterior to the obturator, and in 2 cases anterior to the obturator. The Syed template was then placed and later sutured against the perineum with the distal end of the tandem and obturator extending through the template. The distal end of the superflab bolus was trimmed flush with the introitus for each patient. Needle insertion was completed per the pre-plan and US guidance, traversing the sperflab to reach the target as needed (see Figure 1). After the procedure, each patient underwent CT-based

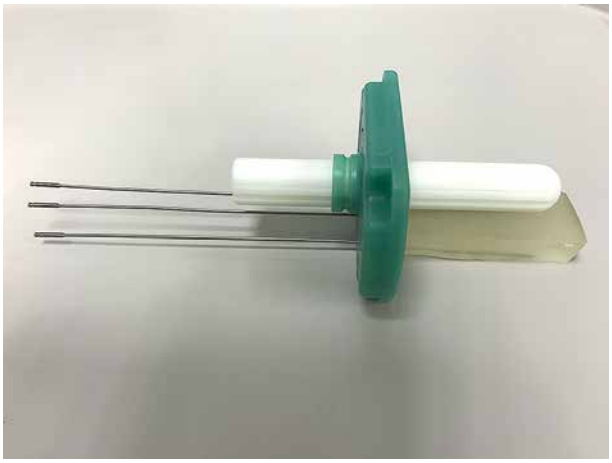

Fig. 1. Configuration showing the spatial relation between the template (green), obturator (white), needles, and superflab when placed for treatment

planning, with prescription doses ranging from 85-90 Gy total EQD_2 when accounting for EBRT. Fractionation was 5-6 Gy per fraction biologically effective dose (BID) over 2-3 days in 1-2 total implants for each patient, depending on tumor bulk. Distances from the prescription isodose line (IDL) to OAR were measured using the measurement tool in Eclipse (Varian Medical Systems, Palo Alto, CA) on axial slices for all OAR except the sigmoid, which was measured on the sagittal view (see Figure 2). A measurement was made of the minimum distance between the regions defined by the prescription IDL and the OAR of interest along a line orthogonal to both by a single observer, examining all slices in which these regions were both present. If an OAR was contained within the region bounded by the prescription IDL, a measurement with a negative value was made of the greatest dimension of the overlapping region between the OAR and the region contained by the prescription IDL.

Statistics

A paired Student's *t*-test was performed on the preplan and implant distances between OAR and the prescription IDL, and EQD_2 fraction-matched brachytherapy point doses (D_{2cc}, D_{1cc}, and $D_{0.1cc}$) for the rectum, sigmoid, bladder, and urethra in each patient. The Bonferroni correction for multiple comparisons was applied to control the family-wise error rate, and an adjusted α of 0.0125 (0.05/4) was used for these tests. Acute toxicities were graded at the end of treatment and at 1 and 3 months post-treatment using the NIH Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Prior to initiating use in patients, the superflab bolus was tested mechanically to determine the possibility of distal displacement of bolus material with needle insertion to confirm that no bolus material would be displaced into patient tissues.

Results

The distances between the closest rectal point to the prescription IDL on the 12 CT pre- (no superflab) and post-implant (with superflab) plans were on average 0.53 cm (range, –0.04-1.30 cm) into the rectum and 0.14 cm (range, –0.26-1.91 cm) away from the rectum, respectively. On average, the superflab insertion resulted in a 0.69 cm displacement of the closest rectal point away from prescription IDL from pre- to post-implant.

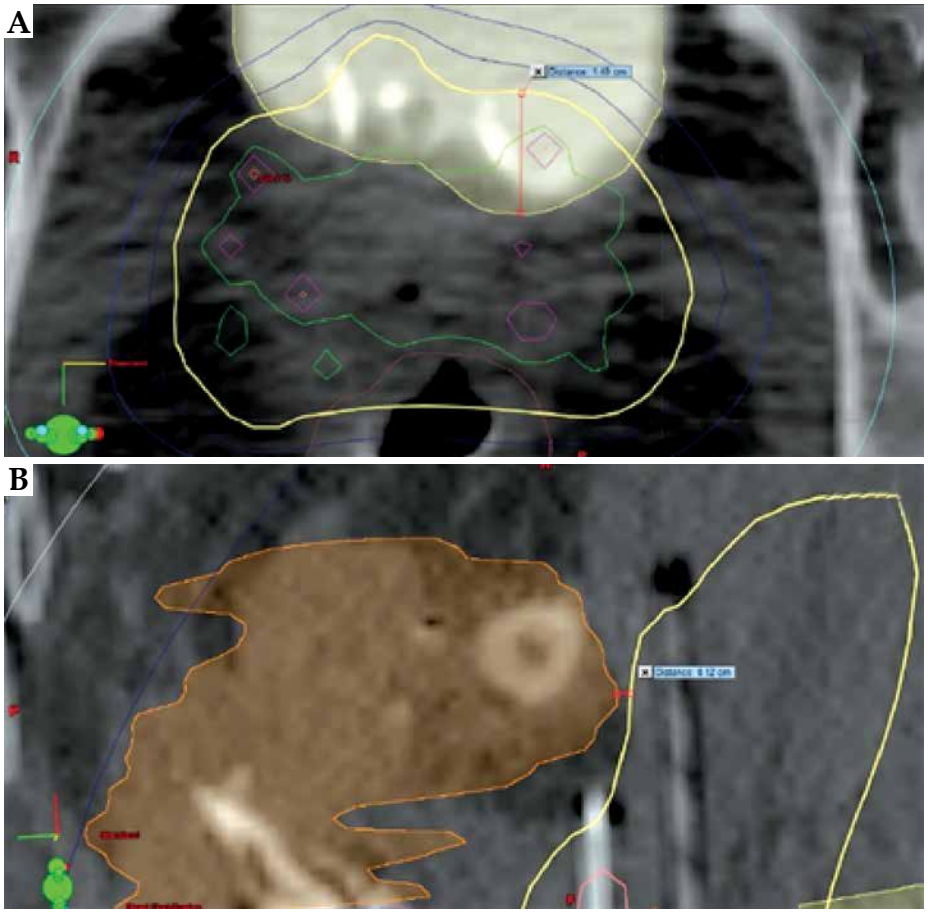

Fig. 2. Example of measurements between organs at risk and prescription isodose line (IDL) for **(A)** the bladder, with a measurement of the maximum extent of the organ into the prescription IDL, **B)** the sigmoid, which was measured on sagittal images. All measurements were made along a line perpendicular to both surfaces at the points of interest. The thick yellow line represents the prescription IDL, the thin yellow line represents the volume of the bladder, and the orange-shaded region represents the volume of the sigmoid

In the pre-implant plans, the bladder was on average 0.77 cm (range, 0.19-1.61 cm) into the region contained by the prescription IDL, and on the post-implant plans the bladder was on average 0.31 cm (range –0.16-0.82 cm) into the region contained by the prescription IDL. The average displacement of the bladder from pre- to post-implant was 0.50 cm away from the prescription IDL.

In the pre-implant plans, the urethra was on average 0.11 cm (range, –1.83-1.85 cm) into the region contained by the prescription IDL, and on the post-implant plans the urethra was on average 0.26 cm (range –0.96-1.96 cm) away from the from the closest point on the prescription IDL. The average displacement of the urethra from pre- to post-implant was 0.22 cm from the prescription IDL.

The average reduction in rectal EQD_2 D_{2cc} between the pre-plan and post-implant plan was 15.8 Gy (range, –2.8-50.9 Gy). The average reduction in bladder EQD_2 D_{2cc} between the pre-plan and post-implant plan was 18.3 Gy (range, –18.5-7.5 Gy). The average reduction in urethral EQD_2 D_{2cc} between the pre-plan and post-implant plan was 4.9 Gy (range, –5.8-37.9 Gy). Distances from the prescription IDL and dosimetry per fraction for other OAR are displayed in Table 2.

Grade 1-2 acute gastrointestinal toxicity was reported in 4/12 patients, and one patient developed a sub-acute rectovaginal fistula requiring surgical evaluation that was anticipated due to direct tumor involvement of the rectovaginal septum. Genitourinary toxicity was grade 0-2 in 5/12 patients acutely, with only 2 patients retaining grade 2 GU toxicity in the subacute follow-up period. One patient developed grade 3 vaginal stenosis in the sub-acute period that limited physical exam. This patient endorsed non-compliance with the use of a vaginal dilator or similar mechanical device to maintain vaginal patency. No patients developed infection or bleeding.

When comparing the EQD_2 D_{90} for the high-risk target volume (HR-TV) between the pre-plan and implants, the median D_{90} as a percentage of the prescription was 104% (range, 58-122%) in the pre-plan and 92% (range, 71-131%) for the implants. There was no significant difference between the median pre-plan and implant EQD_2 $D_{90\%}$ ($p = 0.4$).

Discussion

The addition of brachytherapy to EBRT provides a significant survival benefit in patients with gynecologic

Table 2. Organs at risk displacement and dosimetry

	Pre-implant (no superflab)	Implant (with superflab)	*p* value
Bladder			
Average distance from Rx IDL (cm)	–0.773	–0.312	0.0004***
Average EqD_2 D_{2cc} (Gy, per fraction)	14.82	7.63	0.0004***
Average EqD_2 D_{1cc} (Gy, per fraction)	19.85	9.08	0.00006***
Average EqD_2 $D_{0.1cc}$ (Gy, per fraction)	42.73	12.21	0.0002***
Urethra			
Average distance from Rx IDL (cm)	–0.113	0.264	0.232
Average EqD_2 D_{2cc} (Gy, per fraction)	3.46	2.36	0.04
Average EqD_2 D_{1cc} (Gy, per fraction)	5.21	3.51	0.04
Average EqD_2 $D_{0.1cc}$ (Gy, per fraction)	12.62	5.78	0.014
Rectum			
Average distance from Rx IDL (cm)	–0.530	0.139	0.0005***
Average EqD_2 D_{2cc} (Gy, per fraction)	10.50	5.32	0.00003***
Average EqD_2 D_{1cc} (Gy, per fraction)	13.92	6.40	0.00002***
Average EqD_2 $D_{0.1cc}$ (Gy, per fraction)	25.04	8.05	0.0002***
Sigmoid			
Average Distance from Rx IDL (cm)	0.110	0.524	0.007***
Average EqD_2 D_{2cc} (Gy, per fraction)	5.24	3.46	0.002***
Average EqD_2 D_{1cc} (Gy, per fraction)	6.77	4.28	0.0006***
Average EqD_2 $D_{0.1cc}$ (Gy, per fraction)	25.04	8.05	0.0003***

****Denotes a statistically significant p-value at $\alpha = 0.05$. Bonferroni correction applied to all tests*
IDL – prescription isodose line, EqD_2 – equivalent dose at 2 Gy, D_{2cc}, D_{1cc}, $D_{0.1cc}$ – minimum dose to the most exposed 0.1 cm^3, 1 cm^3, 2 cm^3

cancer, while minimizing toxicity from dose to nearby normal tissues [16]. In patients with locally advanced disease with wide lateral tumor spread, bulky disease, or distorted anatomy, interstitial brachytherapy provides improved dose conformity to the tumor and high-risk regions and improved locoregional control [17,18]. The use of image-guidance in the administration of brachytherapy has been shown in several larger retrospective studies to improve local control and survival even further and led to the suggestion of several key quality parameters to guide treatment technique [1,19,20,21]. MRI-guidance appears to provide improved visualization and delineation of tumor and normal tissues, and subsequently better local control [1,22]. The results of RetroEMBRACE, a multi-institutional, large retrospective cohort analysis of patients with locally advanced cervical cancer treated with EBRT and concurrent chemotherapy followed by image-guided brachytherapy (80.9% receiving MRI-guidance) showed overall 3- and 5-year local control rates at 91 and 85%, respectively [22]. Severe late toxicities (grade 5) were relatively limited at a reported 11% after 5 years, emphasizing the importance of imaging in delineation of target and normal tissues.

Several recent studies analyzing dosimetric parameters in MRI-guided brachytherapy have provided cutoffs for OAR doses that predict significant toxicity. Georg *et al*. suggested in a retrospective study of brachytherapy patients treated with MRI-guidance that a D_{2cc} limit of < 75 Gy for the sigmoid and rectum and < 100 Gy for the bladder were significant thresholds for increased risk of major toxicities [23]. Ribiero *et al*. subsequently reported in a retrospective study that a D_{2cc} > 65 Gy was correlated with grade 3+ late rectal toxicity, suggesting an even more stringent constraint for rectal dose [2]. These data emphasize the importance of the exploration of novel OAR sparing methods in improving outcomes, particularly in interstitial brachytherapy; additional complications may arise in this technique related to the mechanics of traversing normal tissues with needles and catheters to reach the target. Displacement of OAR may be beneficial from a dosimetric perspective, but also allow for avoidance of mechanical trauma to other organs. In cases of complex tumor geometry this may be especially significant when an interstitial approach is typically warranted to achieve adequate tumor coverage (see Figure 3).

Our institutional experience of the use of superflab bolus has shown significant displacement and dose reduction to OAR between the pre-plan and implant parameters in a modern cohort of interstitial brachytherapy patients. We observed dose reductions of up to as much of 5 Gy per fraction in the rectum, with significant differences in average EQD_2 D_{2cc} dose per fraction in both the rectum and bladder. The differences between pre-plan and implant doses to OAR are generally larger in our cohort than is typically reported in other series. We believe that this is due to prioritization of HR-TV coverage in the pre-plan above other constraints leading to exaggerated reductions after vaginal packing and plan finalization with the tandem and needles in place. Optimization for limitation of OAR dose would often occur during the post-implant plan. These optimization goals may also explain the significant increase in bladder distance and reduction in bladder dose despite only 2 patients having superflab placed anteriorly during packing.

Rectal and bladder filling were comparable between pre and post-implant plans and were a strength of the methodology of this study. The use of US guidance and bladder filling facilitated this consistency. The final doses per fraction achieved in both the bladder and rectum were comparable with dosimetry reported in other series

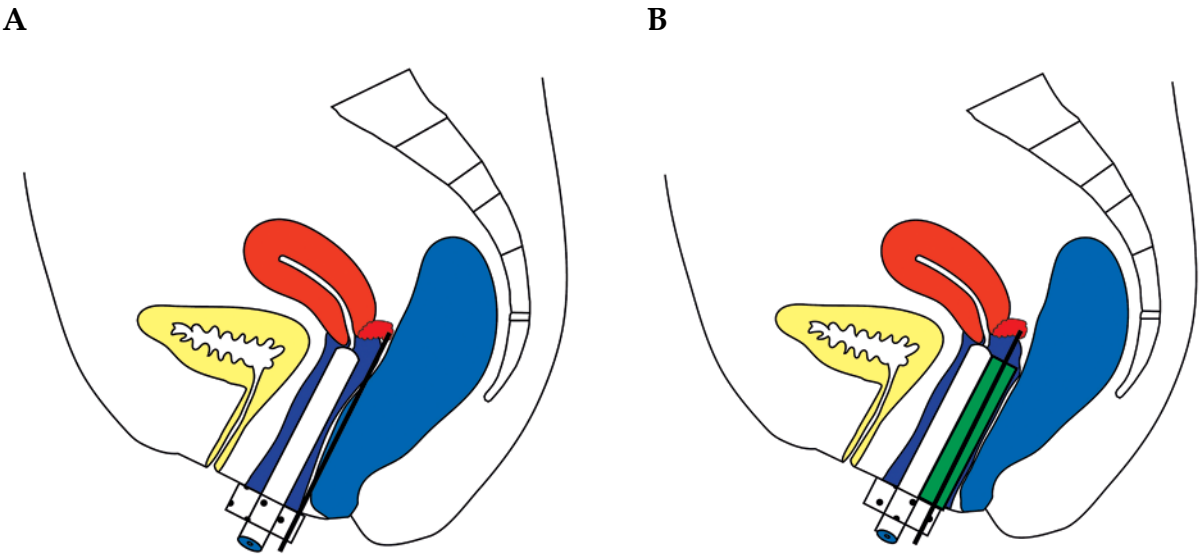

Fig. 3. Sagittal view diagrams showing the challenges associated with tumors with wide lateral spread. The bladder and rectum are shown in yellow and blue, the vaginal canal in purple, uterus in orange, tumor in red, obturator and tandem in white, superflab in green, and catheter trajectory in black. The template is shown with a spotted pattern. To reach the posterior portion of the tumor, catheter placement requires traversing the rectal mucosa. **A)** shows the needle trajectory without superflab, and **B)** with superflab in place

exploring the use of other OAR displacement techniques such as rectal retractors or gauze packing, when adjusted for the prescribed dose per fraction. Gaudet *et al*. reported a study on the use of vaginal gauze packing with and without a rectal retractor in the treatment of primarily stage I and II cervical cancer with image-guided intracavitary brachytherapy using a tandem and ring system. Mean bladder D_{2cc} using gauze alone and with a retractor were 4.44 and 4.43 Gy per fraction, respectively, and mean rectal D_{2cc} with gauze alone and with a retractor were 2.84 and 2.41 Gy, respectively [24]. Rai *et al*. reported a randomized study comparing the use of a bladder-rectum spacer balloon to vaginal gauze packing in the treatment of patients with cervical cancer with intracavitary brachytherapy using a tandem and ovoid system. Mean bladder D_{2cc} was reported as 8.08 Gy for gauze packing and 8.20 Gy for the spacer balloon. Mean rectal D_{2cc} was reported as 5.06 Gy and 4.64 Gy for gauze and the spacer balloon, respectively [25]. These studies used non-interstitial techniques, and any direct comparison of dosimetry or extrapolation should be made with caution. The per fraction doses in our study were higher than those reported in Gaudet, likely due to the predominance of early stage disease in their cohort. The small size of our sample also presents susceptibility to the weakness of influential outliers that may have had more extensive pre-rectal disease, resulting in a greater mean rectal dose. Our results are comparable to the dosimetry seen in Rai with the use of both gauze and balloon packing. Direct comparison of the per fraction doses to OAR with other studies that used an interstitial technique are difficult to perform, as many reports do not include the OAR displacement technique or the specific contribution of brachytherapy to the total OAR dose.

Acute and sub-acute toxicities were limited; 2 patients experienced grade 3 toxicity (rectovaginal fistula and vaginal stenosis), and both had other factors related to their disease or therapeutic compliance pre-disposing them to these toxicities. 4/12 patients experienced acute grade 1-2 GU toxicities, and 5/12 had sub-acute toxicity at 3 months. 4/12 patients experienced acute grade 1-2 rectal complications, with only 2/12 having persistent grade 1 toxicity at 3 months. 4/12 patients also experienced grade 1-2 skin and vaginal toxicities that persisted at 3 months. These rates are comparable to other reported series, which have shown rates of acute toxicity of any type between 27-48% [17,26]. There was no significant difference in average $D_{90\%}$ between the pre-plans and implants; this demonstrated achievement of our goal of not compromising target coverage, while trying to limit OAR dose between the pre-plan and implant.

Data regarding upper dose limits specifically for interstitial brachytherapy and critical dosimetric factors predictive of toxicity are inconsistent, due in part to the paucity of cases and lack of multi-institutional data. The complex nature of treatment with interstitial technique and various unique patient factors that contribute to the development of toxicity make comparisons of toxicity profile across institutions difficult. Sigmoid toxicity appears to be relatively rare compared to the rectum and bladder, and is often difficult to distinguish from rectal toxicity. The rectum and bladder are typically in closer apposition to the cervix, parametrium, and the vaginal canal, and thus exposed to higher doses. EQD_2 D_{2cc} to the rectum and rectal mucosa appears to be a consistent predictive factor for rectal toxicity across several larger retrospective studies [13,27,28]. Lee *et al*. found that the magnitude of the D_{2cc} rectum was predictive for late rectal toxicity, and that large target volumes were associated with grade 3-4 rectal toxicity [13]. Amsbaugh *et al*. conducted a retrospective study with locally advanced gynecologic cancers treated with both LDR and HDR interstitial brachytherapy, and found that the $D_{0.1cc}$ to the urethra was predictive of severe urinary toxicity, with a EQD_2 dose of 23.1 Gy yielding a 10% probability of grade 3 urinary toxicity [28]. The preponderance of retrospective data and case reports highlight the importance of sparing OAR using techniques like retraction or vaginal packing when possible.

The variability in vaginal packing technique across different institutions is a natural product of the complexity of interstitial technique. Additionally, the relative rarity of cases of interstitial brachytherapy makes head-to-head comparisons of these techniques difficult to power. This is reflected in the recommendations on packing in the consensus guidelines from the American Brachytherapy Society [29,30]. The 2000 guidelines on HDR brachytherapy for carcinoma of the cervix recommend only the use of vaginal packing with per fraction adjustment to maintain optimal positioning of the applicator and OAR [30]. The updated 2012 guidelines remove any explicit mention of packing in favor of a broader suggestion that "(…) protocol consistency within an institution will help to avoid error (…)". In the absence of data to support a more specific guideline, institutional consistency and sharing of viable methods for improving sparing of OAR during brachytherapy is critical for giving practitioners options that may provide an advantage in the sparing of normal tissues and subsequent reduction in treatment toxicity.

Conclusions

Our initial experience with superflab as a vaginal packing material demonstrates technical feasibility and dosimetric improvement for OAR without compromising coverage of the HR-TV. We submit that the use of superflab is a reproducible, easily implemented, and low-cost alternative for vaginal packing in interstitial brachytherapy that warrants further study.

Disclosure

The authors report no conflict of interest.

References

1. 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 cervical cancer. *Radiother Oncol* 2011; 100: 116-123.
2. Ribeiro I, Janssen H, De Brabandere M et al. Long term experience with 3D image guided brachytherapy and clinical outcome in cervical cancer patients. *Radiother Oncol* 2016; 120: 447-454.
3. Pötter R, Haie-Meder C, Van Limbergen E et al. Recommendations from gynaecological (GYN) GEC ESTRO working

group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy – 3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006; 78: 67-77.
4. Tanderup K, Potter R, Lindegaard J et al. Image Guided Intensity Modulated External Beam Radiochemotherapy and MRI Based Adaptive Brachytherapy in Advanced Cervical Cancer. EMBRACE II Study Protocol v1.0. Available at: www.embracestudy.dk
5. Malaker K, Shukla V, D'Souza H et al. Minimizing urinary bladder radiation dose during brachytherapy for carcinoma of the cervix using balloon inflation technique. *Int J Radiat Oncol Biol Phys* 2005; 61: 257-266.
6. Eng TY, Fuller CD, Cavanaugh SX et al. Significant rectal and bladder dose reduction via utilization of Foley balloon catheters in high-dose-rate tandem and ovoid intracavitary brachytherapy of the uterine cervix. *Int J Radiat Oncol Biol Phys* 2004; 59: 174-178.
7. Saini AS, Zhang GG, Finkelstein SE et al. Dose reduction study in vaginal balloon packing filled with contrast for HDR brachytherapy treatment. *Int J Radiat Oncol Biol Phys* 2011; 80: 1263-1267.
8. Khan FM, Gibbons JP. Dose Distribution and Scatter Analysis. In: Khan FM, Gibbons JP (eds.). The Physics of Radiation Therapy. 5th ed. Lippincott Williams & Wilkins, Philadelphia 2014; 139-141.
9. Rai B, Patel FD, Chakraborty S et al. Bladder-Rectum Spacer Balloon versus Vaginal Gauze Packing in High Dose Rate Brachytherapy in Cervical Cancer: A Randomised Study (Part II). *Clin Oncol (R Coll Radiol)* 2015; 27: 713-719.
10. De Ieso PB, Mullassery V, Shrimali R et al. Image-guided Vulvovaginal Interstitial Brachytherapy in the Treatment of Primary and Recurrent Gynecological Malignancies. *Brachytherapy* 2012; 11: 306-310.
11. Beriwal S, Rwigema JCM, Higgins E et al. Three-dimensional Image-based High-dose-rate Interstitial Brachytherapy for Vaginal Cancer. *Brachytherapy* 2012; 11: 176-180.
12. Thibault I, Lavallée MC, Aubin S et al. Inverse-planned gynecologic high-dose-rate interstitial brachytherapy: clinical outcomes and dose-volume histogram analysis. *Brachytherapy* 2012; 11: 181-191.
13. Lee LJ, Viswanathan AN. Predictors of toxicity after image-guided high-dose-rate interstitial brachytherapy for gynecologic cancer. *Int J Radiat Oncol Biol Phys* 2012; 84: 1192-1197.
14. Viswanathan AN, Moughan J, Small W et al. The quality of cervical cancer brachytherapy implantation and the impact on local recurrence and disease-free survival in radiation therapy oncology group prospective trials 0116 and 0128. *Int J Gyn Cancer* 2012; 22: 123-131.
15. Radiation Products Design, Inc. Radiation Products Design. Superflab Bolus, 0.5 cm Thick X 30 cm Square. Available at: http://www.rpdinc.com/superflab-bolus-05cm-thick-x-30cm-square-1696.html
16. Logsdon MD, Eifel PJ. FIGO IIIB squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy. *Int J Radiat Oncol Biol Phys* 1999; 43: 763-775.
17. Pinn-Bingham M, Puthawala AA, Syed AM et al. Outcomes of High-Dose-Rate Interstitial Brachytherapy in the Treatment of Locally Advanced Cervical Cancer: Long-term Results. *Int J Radiat Oncol Biol Phys* 2013; 85: 714-720.
18. Syed AMN, Puthawala AA, Abdelaziz NN et al. Long-term Results of Low-dose-rate Interstitial-intracavitary Brachytherapy in the Treatment of Carcinoma of the Cervix. *Int J Radiat Oncol Biol Phys* 2002; 54: 67-78.
19. Dimopoulos JCA, Lang S, Kirisits C et al. Dose-Volume Histogram Parameters and Local Tumor Control in Magnetic Resonance Image-Guided Cervical Cancer Brachytherapy. *Int J Radiat Oncol Biol Phys* 2009; 75: 56-63.
20. Dimopoulos JCA, Pötter R, Lang S et al. Dose-effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy. *Radiother Oncol* 2009; 93: 311-315.
21. Rijkmans EC, Nout RA, Rutten IH et al. Improved Survival of Patients with Cervical Cancer Treated with Image-guided Brachytherapy Compared with Conventional Brachytherapy. *Gyn Oncol* 2014; 135: 231-238.
22. Sturdza A, Pötter R, Fokdal LU et al. Image Guided Brachytherapy in Locally Advanced Cervical Cancer: Improved Pelvic Control and Survival in RetroEMBRACE, a Multicenter Cohort Study. *Radiother Oncol* 2016; 120: 428-433.
23. Georg P, Lang S, Dimopoulos JC et al. Dose-volume histogram parameters and late side effects in magnetic resonance image-guided adaptive cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2011; 79: 356-362.
24. Gaudet M, Lim P, Yuen C et al. Comparative analysis of rectal dose parameters in image-guided high-dose-rate brachytherapy for cervical cancer with and without a rectal retractor. *Brachytherapy* 2014; 13: 257-262.
25. Rai B, Patel F, Chakraborty S et al. Bladder-rectum spacer balloon in high-dose-rate brachytherapy in cervix carcinoma. *Int J Radiat Oncol Biol Phys* 2013; 85: 217-222.
26. Bailleux C, Falk AT, Chand-Fouche ME et al. Concomitant cervical and transperineal parametrial high-dose-rate brachytherapy boost for locally advanced cervical cancer. *J Contemp Brachytherapy* 2016; 8: 23-31.
27. Chopra S, Dora T, Engineer R et al. Late rectal toxicity after image-based high-dose-rate interstitial brachytherapy for postoperative recurrent and/or residual cervical cancers: EQD2 predictors for Grade ≥ II toxicity. *Brachytherapy* 2015; 14: 881-888.
28. Amsbaugh, MJ, Bhatt N, Hunter T et al. Computed tomography-planned interstitial brachytherapy for locally advanced gynecologic cancer: outcomes and dosimetric predictors of urinary toxicity. *Brachytherapy* 2016; 15: 49-56.
29. Viswanathan AN, Beriwal S, De Los Santos JF et al. American Brachytherapy Society Consensus Guidelines for Locally Advanced Carcinoma of the Cervix. Part II: High-dose-rate Brachytherapy. *Brachytherapy* 2012; 11: 47-52.
30. Nag S, Erickson B, Thomadsen B et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000; 48: 201-211.