



Brachytherapy: A critical component of primary radiation therapy for cervical cancer

From the Society of Gynecologic Oncology (SGO) and the American Brachytherapy Society (ABS)

Christine H. Holschneider^{a,*}, Daniel G. Petereit^b, Christina Chu^c, I-Chow Hsu^d, Yevgeniya J. Ioffe^e, Ann H. Klopp^f, Bhavana Pothuri^g, Lee-may Chen^h, Catheryn Yasharⁱ

^a Gynecologic Oncology, Olive View-UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States of America

^b Radiation Oncology, Regional Health – John T. Vucurevich Cancer Care Institute, Rapid City, SD, United States of America

^c Gynecologic Oncology, Fox Chase Cancer Center, Philadelphia, PA, United States of America

^d Radiation Oncology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, United States of America

^e Gynecologic Oncology, Loma Linda University, Loma Linda, CA, United States of America

^f Radiation Oncology, MD Anderson Cancer Center, Houston, TX, United States of America

^g Gynecologic Oncology, NYU Langone Laura and Isaac Perlmutter Cancer Center, New York, NY, United States of America

^h Gynecologic Oncology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, United States of America

ⁱ Radiation Oncology, UC San Diego School of Medicine, San Diego, CA, United States of America

HIGHLIGHTS

- Decline in brachytherapy parallels increase in IMRT/SBRT boosts.
- Less brachytherapy is coupled with increased mortality.
- CT/MRI adaptive brachytherapy is preferred.
- EBRT & brachytherapy can be delivered at different institutions without compromising outcome.

ARTICLE INFO

Article history:

Received 28 August 2018

Received in revised form 11 October 2018

Accepted 15 October 2018

Available online 18 January 2019

Keywords:

Cervical cancer

Brachytherapy

SBRT

IMRT

Primary chemoradiation

ABSTRACT

Brachytherapy is well-established as an integral component in the standard of care for treatment of patients receiving primary radiotherapy for cervical cancer. A decline in brachytherapy has been associated with negative impacts on survival in the era of modern EBRT techniques. Conformal external beam therapies such as intensity modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT) should not be used as alternatives to brachytherapy in patients undergoing primary curative-intent radiation therapy for cervical cancer. Computed tomography or magnetic resonance image-guided adaptive brachytherapy is evolving as the preferred brachytherapy method. With careful care coordination EBRT and brachytherapy can be successfully delivered at different treatment centers without compromising treatment time and outcome in areas where access to brachytherapy may be limited.

© 2018 Elsevier Inc. and American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

1. History of cervical cancer treatment and introduction of brachytherapy

Cervical cancer is the fourth most common cancer worldwide with an estimated 528,000 new cases and 266,000 deaths annually [1]. Modern treatment of the disease has evolved substantially since the end of

the 19th century, which saw reports of the first radical hysterectomies described by Clark and Wertheim. The mortality rate for Dr. Wertheim's procedure was 18% with a major morbidity rate of 31% [2]. The Curies' discovery of radium in 1898 opened the door for Dr. Robert Abbe who was the first to apply radium for the treatment of cervical cancer in 1905, and by 1912, Dr. Gösta Forsell reported using radium to achieve

* Corresponding author at: Olive View-UCLA Medical Center, 14445 Olive View Drive, Room 6D-116, Sylmar, CA 91342, United States of America.
E-mail address: cholschneider@dhs.lacounty.gov (C.H. Holschneider).

“clinical healing” in patients with inoperable disease [3]. Abbe was the first to report a cure in 1913 [4,5]. Over the subsequent decades, a handful of medical centers developed the fundamental “systems” of intracavitary radiation therapy, including Paris, Stockholm, Manchester, Munich, and the MD Anderson Cancer Center in Houston, which designed the Fletcher system in the 1940s [5,6]. These applicators made it possible to position the radioactive sources adjacent to the cervix with intrauterine and intravaginal applicators. The steep dose drop off of radioactive sources made it possible to deliver higher doses to the cervix without exceeding the dose tolerance of adjacent normal tissues and adjacent organs. By the 1970s, brachytherapy was in widespread use for the treatment of cervical cancer.

2. Evidence for essential benefit of brachytherapy in cervical cancer

In 1991, Lanciano et al. issued a final report of the 1973 and 1978 Patterns of Care Studies in the United States, which included data from 1558 patients with squamous cell carcinoma of the cervix treated at centers across the country [7]. The only treatment factor associated with improved pelvic control of disease on multivariate analysis was the use of intracavitary radiation ($p < 0.001$). Higher dose to the cervix, estimated as the dose to point A, was strongly associated with improved survival ($p < 0.001$). This study established the national goal of dose intensification through the use of brachytherapy to improve radiation outcome for patients with cervical carcinoma.

The current standard primary radiation treatment of locoregional (stage IB–IVA) cervical cancer consists of external beam radiation with concurrent cisplatin-based chemotherapy plus brachytherapy [8–12]. Numerous studies have shown that brachytherapy is an essential component for curative intent radiation and is strongly correlated with higher rates of survival [13–15]. A study of 907 patients with stage IIIB cervical cancer who completed radiation treatment with curative intent demonstrated that the 641 patients who underwent intracavitary radiation treatment had an improved disease specific survival of 45% at 5 years compared with only 24% for the 266 patients treated with external beam radiation therapy alone [16]. Similar results were seen in a more recent retrospective study comparing outcomes for cervical cancer patients treated with or without brachytherapy. Cancer specific survival was significantly higher (68.5% vs 35.4% after 5 years) for patients that received brachytherapy as compared to those that received an external beam boost in place of brachytherapy [17].

In 2012, the American Brachytherapy Society consensus guidelines affirmed the essential curative role of tandem based brachytherapy in cervical cancer [18]. The National Comprehensive Cancer Network also emphasizes brachytherapy as standard of care and explicitly states that conformal external beam therapies should not be used as alternatives to brachytherapy for the treatment of central disease in patients with an intact cervix [19]. Hallmarks of quality cervical cancer brachytherapy are summarized in Table 1.

3. Image-guided brachytherapy

Historically, brachytherapy was delivered using 2-D dosimetry with the guidance of anteroposterior (AP) and lateral X-rays to assess applicator position and estimate dose to the cervix with point A, representing a paracervical reference point where the uterine vessels are estimated to cross the ureter. The dose to the bladder was estimated based on the position of the Foley bulb and the rectum by measuring 5 mm posterior to vaginal ovoids or packing [20,21]. In the past two decades, image guided brachytherapy (IGBT) has been introduced which uses CT or MRI to optimize dose to the cervix and reduce dose to normal tissues using 3-D based volumetric planning. IGBT makes it possible to improve tumor coverage while sparing the adjacent surrounding tissues. Introduction of MRI-based brachytherapy planning allows for improved tumor visualization over CT due to excellent soft tissue imaging characteristics and reliable volumetric definition of the target, thereby,

improving the dose distribution with regards to both volume and time. Repetitive imaging performed with each brachytherapy treatment allows for adaptation of the radiation dose to the individual patient's tumor anatomy accounting for tumor regression as it occurs during treatment, while sparing surrounding structures. The improvement in the therapeutic ratio with IGBT results from either limiting the classic Point A distribution by “pulling in” the isodose curves or expanding them with the use of interstitial catheters. In 2016, Mazon et al. evaluated 13 series treating 1299 patients and demonstrated a dose response in cervical cancer, with the probability of control increasing with the D90 (dose to 90% of the target volume). A D90 of 81.4 Gy was associated with a 90% chance of local control [22]. Newer GYN applicators with intra-vaginal interstitial needles allow the brachytherapist to expand the lateral tumor extension into the medial parametria with potentially lower toxicities compared to the transperineal approach with a Syed template; at times the standard template is more appropriate with large volume disease. Based on the experience to date, IGBT using either CT or MRI has the potential to result in concomitant decrease in the rates of local failure and in reduced morbidity, thus significantly impacting overall clinical outcome. Detailed instructions and fractionation schemes for intracavitary and interstitial therapy, as well as schools to hone expertise, are provided by the American Brachytherapy Society on a regular basis (www.americanbrachytherapy.org).

The clinical evidence supporting IGBT comes from numerous retrospective and prospective studies published in the past decade [23]. The international RetroEMBRACE study involved a retrospective study of 731 patients from 12 centers [24]. This study provided key data supporting advanced image-based brachytherapy for large tumors with a 10% improvement in pelvic control (87% vs. 77%) for patients treated with IGBT when compared with historic results of a meta-analysis of 13 RCTs involving 3128 patients treated with EBRT, chemo sensitization and standard 2-D brachytherapy [25]. In RetroEMBRACE, stage-specific 3-year local failure rates were 2%, 7%, and 21% for stages IB, IIB, and IIIB, respectively, and the promise of image guided brachytherapy is to increase local control. Late morbidity was lower with IGBT, despite the higher doses delivered to the high-risk clinical target volume (HR-CTV) with IGBT. RetroEMBRACE reported actuarial 5-year grade 3–5 toxicity rates of 5% for bladder, 7% for gastrointestinal tract, and 5% for vagina [24]. The prospective non-randomized STIC study compared 2-D vs 3-D brachytherapy dosimetry in 705 patients [26], finding that 3-D image guided brachytherapy was associated with improved local relapse-free survival at 24 months compared to 2-D imaging (78.5% vs. 73.9%). Furthermore, patients who were treated with image guided brachytherapy had a substantially lower grade 3–4 toxicity rate (2.6% vs. 22.7%) [26]. The prospective multicenter observational EMBRACE study (International study on MRI guided BRachytherapy in local Advanced Cervical cancer) enrolled 1412 patients with locally advanced cervical cancer who received MR based image guided brachytherapy. Analysis of this data set identified critical dose-volume predictors for urinary and rectal morbidity [27]. A retrospective study comparing 56 patients undergoing MR-guided versus CT-guided high dose rate interstitial brachytherapy for advanced cervical cancer, suggests the superiority of MR-based planning which resulted in improved

Table 1

Hallmarks of quality cervical cancer brachytherapy
✓ Use of intracavitary and/or interstitial applicators which allow radiation sources to approximate the target volume
✓ Timely incorporation of brachytherapy with external beam radiation to complete all radiation treatment within 8 weeks
✓ Image guidance with ultrasound, CT or MRI to evaluate applicator position
✓ Optimized dosimetry with CT or MRI to deliver sufficient dose to tumor target while respecting normal tissue doses
✓ Treatment delivery with 1–2 low dose rate/pulsed dose rate (LDR/PDR) or 4–6 high dose rate (HDR) brachytherapy treatments

overall survival (OS) of 84% vs 56%, with no difference in toxicity [28]. In 2012, the GEC-ESTRO (Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology) published MR-based post implant guidelines to aid practitioners in tumor delineation and defining target volumes and organs at risk [29].

4. Decline in brachytherapy and the associated negative impact on survival in the era of modern EBRT techniques

Despite the strong evidence demonstrating the benefit of brachytherapy, its usage has been declining over the past decade. This decline in brachytherapy may be a result of the expansion of conformal external beam radiation therapy techniques, most notably intensity modulated radiation therapy (IMRT), over the past 2 decades. Utilizing inverse planning and multileaf collimators with computerized optimization it is possible to plan and deliver highly conformal radiation therapy. Early reports showed low toxicity despite higher delivered doses in comparison to conventional external beam therapy [30,31]. IMRT use more than doubled between 2002 and 2004 from 32.0% to 67.8% [32]. One use of IMRT has been to escalate the dose to the cervix to forgo brachytherapy when looking at patterns of radiotherapy practice [33]. Unfortunately, recent studies have shown a substantial decrease in the utilization of brachytherapy for locally advanced cervical cancer with associated worsening survival outcomes. There are indications that perhaps the replacement of brachytherapy with external techniques could be one of the causes.

In 2013, Han et al. reported the first population-based analysis demonstrating a concerning decline in brachytherapy utilization. In this SEER database study of 7359 patients with stage IB2 to IVA cervical cancer treated with EBRT between 1988 and 2009, the authors report a decrease in brachytherapy utilization rate from 83% in 1988 to 58% in 2009. In the same study, brachytherapy treatment was independently associated with better cause-specific (HR 0.64; 95% CI 0.57–0.71), and overall survival (HR 0.66; 95% CI 0.60–0.74) [34]. In a Quality Research in Radiation Oncology (QRRO) study, the proportion of patients that did not receive brachytherapy doubled from 6.4% in the 1996–1999 survey [30] to 12.5% in the 2005–2007 survey [35]. Notably, 65% of patients began treatment in a facility that treated 3 or fewer eligible patients per year and only 8% of US facilities were estimated to treat on average more than 3 patients with intact cervical cancer annually. Another population-based study by Gill et al. utilized the National Cancer Database to evaluate trends in brachytherapy and alternative radiation therapy utilization for 7654 patients treated between January 2004 and December 2011 for stage IIB-IVA cervical cancer. The authors reported a decrease in brachytherapy use from 96.7% in 2004 to 86.1% in 2011, while IMRT and SBRT use increased from 3.3% to 13.9% in the same period. In multivariable survival analyses, IMRT or SBRT boost resulted in inferior OS (HR 1.86; 95% CI 1.35–2.55) as compared with brachytherapy. Of note, in this study the survival detriment associated with IMRT or SBRT boost was stronger than that associated with not receiving chemotherapy (HR 1.61; 95% CI 1.27–2.04), further underscoring the importance of brachytherapy as a critical treatment component for locally advanced cervical cancer (Fig. 1) [36]. As a follow up to Gill et al., Robin and colleagues examined 15,194 women with locally advanced cervical cancer from the National Cancer Database. Only 44.3% of patients received standard of care treatment. Factors associated with likelihood of receiving standard of care therapy included treatment at high volume centers, academic centers, and comprehensive community cancer centers. Patients with private insurance and higher income also were more likely to receive standard of care. Only 49.5% of patients received EBRT with brachytherapy. Although an EBRT boost derived better outcome than no boost, patients receiving brachytherapy demonstrated superior OS (HR 0.554, $p < 0.001$). The authors describe a troubling trend where fewer than half of patients received appropriate standard of care treatment with brachytherapy despite superior outcomes and further highlight disparities in healthcare delivery [37]. The

American College of Surgeons Commission on Cancer recognizes cancer care programs for providing high quality, multidisciplinary, patient centered care. Standard 4.1 evaluates compliance with national treatment guidelines. Use of brachytherapy in patients treated with primary radiation with curative intent for cervical cancer is one of the surveillance measures recently introduced. In 2015, only 67.5% of all Commission on Cancer approved programs were estimated to be in compliance [38]. This again highlights the importance of education and dissemination of knowledge that brachytherapy is a critical component of curative intent treatment for locally advanced cervical cancer.

5. Comparison of brachytherapy with IMRT or SBRT

The trends of declining brachytherapy utilization have occurred despite poor outcomes noted with IMRT and SBRT as potential substitutes for brachytherapy. In one study IMRT demonstrated a lower equivalent biologic effective dose (BED) compared to brachytherapy and poorer outcomes [39]. There have been efforts to investigate SBRT as a potential alternative to brachytherapy as well. Initially, dosimetric analyses have evaluated dose target coverage and dose to normal organs such as rectum, bowel, and bladder and compared those to HDR brachytherapy [40,41]. The clinical experiences with SBRT for women who are medically unable to undergo brachytherapy or who refuse brachytherapy have been published [42–48], but the series are small and with short follow-up for definitive conclusions. A prospective phase II trial included 28 patients with cervical cancer 77.5% of whom achieved a complete radiographic response at 2 years with no grade 3 or greater urinary or bowel toxicities [42]. A series of 11 patients treated with an external beam boost of 30 Gy in 5 fractions showed no grade 3 or higher GI or GU toxicity and no local recurrences at 6 months of follow up [44]. Another experience of 6 patients treated with a 19.5–20 Gy boost in 3–5 fractions using SBRT had no local or distant recurrences and no grade 3–4 rectal or bladder toxicity at 14 months of follow up [13]. It is important to note that these are small studies and limited to patients who were not candidates for or refused brachytherapy, and there has been no direct comparison to brachytherapy. What is also apparent is that brachytherapy gives a higher central radiation dose when compared to the external technique [49,50], which cannot be reproduced with SBRT or IMRT. Although a distinct advantage of brachytherapy, whether this higher central radiation dose provides a crucial clinical difference has not been

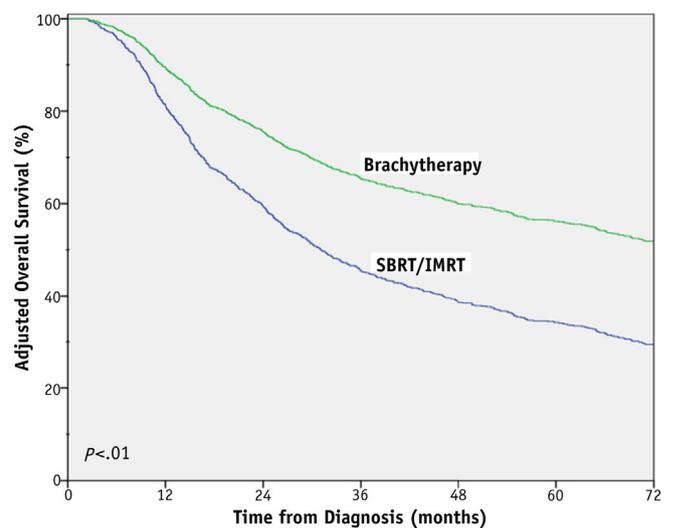


Fig. 1. Adjusted overall survival by boost modality (brachytherapy vs. IMRT/SBRT) as corrected for age, Charlson/Deyo comorbidity score, stage, and chemotherapy utilization. (Reprinted from Gill BS, Lin JF, Krivak TC, et al. National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements. *Int J Radiat Oncol Biol Phys* 2014; 90:1083–90; with permission from Elsevier.)

rigorously tested. No direct comparison between SBRT and brachytherapy has been published. However, the preponderance of data suggests that brachytherapy can deliver significantly higher doses of radiation to the primary tumor, while sparing normal tissues compared to conformal IMRT or SBRT.

Despite insufficient evidence that IMRT or SBRT constitute an equivalent technique to brachytherapy, the national database studies indicate a disturbingly high rate of their usage in lieu of brachytherapy [33–37] and thus non-adherence to established criteria for high-quality primary radiation treatment for cervical cancer. The declining utilization of brachytherapy observed in the studies parallels an incrementally increased use of IMRT and SBRT as a boost and this apparent trade-off is coupled with increased mortality risk suggesting that women are harmed by the substitution. Exploration into why practitioners choose external techniques over brachytherapy is ongoing but some postulations include the time efficiency of external techniques, lack of education or comfort with the more invasive brachytherapy techniques and declining reimbursement for brachytherapy, especially in the outpatient/free-standing setting, and challenges in the coordination of care between Radiation Oncologists and Gynecologic Oncologists for procedures such as an intracervical Smit sleeve or interstitial radiation template placement.

In summary, external beam radiation therapy combined with high quality brachytherapy has been an established treatment course for women with locoregional cervical carcinoma for nearly 100 years. Advances including the use of chemotherapy and image guided brachytherapy have shown promise to increase the number of women cured and decrease the number of women harmed. Despite this, recent data has suggested that other modalities unproven to be equivalent to these tried and true techniques are being increasingly utilized in some centers. Given the lack of sound data demonstrating that modern EBRT techniques including IMRT and SBRT have non-inferior treatment outcomes to brachytherapy, these techniques should not replace brachytherapy in the curative treatment of cervical cancer outside of a clinical trial.

6. Barriers to performance of brachytherapy

There are many potential barriers to timely performance of brachytherapy. Brachytherapy, like any other complex medical procedure, requires training and expertise for optimal application. Evidence suggests there has been a decrease in resident exposure to brachytherapy procedures during training. An analysis of the Accreditation Council of Graduate Medical Education (ACGME) resident case logs showed a 12% decrease in the mean number of total brachytherapy procedures performed per resident during the period between 2006 and 2011 [51], which is presumably paralleled by a similar decrease in exposure of Gynecologic Oncology trainees to brachytherapy procedures. Furthermore, maintenance of brachytherapy skills requires a minimum level of continuous experience after training [15]. In most practices, the number of new cases is insufficient to provide adequate experience. It has been estimated that 50% of facilities treat less than 3 cervical cancer patients per year [33]. Low patient numbers are also associated with lower brachytherapy utilization, increased rates of complication, lower dose to the tumor, and longer average time to complete treatment [33,52–54]. Interstitial brachytherapy is a specialized technique using needles to deliver brachytherapy when the tumor has not shrunk sufficiently for intra-cavitary tandem and ovoid/ring brachytherapy. The American Brachytherapy has schools, guidelines, and fellowships available for those practitioners who want or need more experience in these techniques (www.americanbrachytherapy.org). While gynecologic oncologists can assist in placement of the needles intraoperatively, sufficient practitioner and physics expertise is needed in a department to allow safe delivery. If this is not available timely referral to a center of expertise is advised. All these factors have been shown to adversely influence patient outcome [16,33,52–54].

Limited access to physicians with adequate training and expertise ultimately limits patient access to quality care. In a study of quality for insured patients with intact cervical cancer, only 25% of the patients received treatment which complied with all 3 benchmarks (use of brachytherapy, chemotherapy, and overall treatment time < 63 days) for quality [55]. The study found high quality care was associated with geographic locations with a higher density of practicing radiation oncologists; this may have served as a surrogate marker of access to multidisciplinary resources needed to coordinate all components of complex multimodality treatment.

Another study from Virginia utilized a statewide database to examine effects of tumor-related, demographic, and geospatial factors on the receipt of indicated therapies and mortality in patients with stage IB2–IVA cervical cancer. In a cohort of 1048 patients, the authors identified a low rate of complete quality care in a low volume facility setting [56]. Limited access to brachytherapy is not unique to the US. A survey of all Canadian radiation oncologists suggested a mismatch between demand and availability of brachytherapy programs across Canada. The study concluded that a rational approach to investment in brachytherapy is needed to deliver high-quality treatment [57].

There is concern that the current Medicare reimbursement policy may actually disincentivize physicians to perform brachytherapy for cervical cancer, as reimbursement, especially in free-standing centers, has continued to decline. Since physician reimbursement is often linked to annual RVUs, this presents a potential financial disincentive against brachytherapy delivery. The situation only worsens as brachytherapy becomes increasingly more complex and time-consuming in the era of individualized, image-guided treatment, without a commensurate increase in recognition of the increased complexity.

7. Focused recognition in brachytherapy, maintenance of certification (MOC), and maintaining brachytherapy skills

The American Board of Radiology (ABR) and the American Brachytherapy Society (ABS) are keenly aware of the challenges facing newly trained radiation oncologists as many do not have significant cervical cancer brachytherapy experience [51]. Options for these newly trained physicians include the ABS GYN schools, visiting another institution for more experience, performing an ABS “fellowship,” a fellowship offered at select institutions, or being proctored in their own institution if there is an experienced brachytherapist available. If none of these options are feasible, patients should be referred to a higher volume GYN center with brachytherapy expertise. Replacing brachytherapy with IMRT or SBRT is strongly discouraged as to date the outcomes are inferior [36,58].

The ABS has conducted several successful GYN schools to implement MRI-guided brachytherapy as the supporting evidence from Europe is profound [24,59,60]. In part due to these ABS schools, the number of brachytherapists using MRI-guided brachytherapy planning has increased from 2% in 2007 to 34% in 2014 per the last ABS survey and continues to rise [6]. This supports the notion that centers with expertise can facilitate teaching and implementation of brachytherapy practices.

The ABR implemented a Focused Recognition in Brachytherapy in 2011, as there are no Accreditation Council for Graduate Medical Education (ACGME) approved brachytherapy fellowship programs [61]. The centerpiece of the project was a National Brachytherapy Registry which was to serve as a longitudinal database for participants and the profession. Due to the initial complexity of the website, limited participation, and expense, the ABR unfortunately closed the program. As noted by Wallner et al., “if similar programs were to be considered, participants must perceive real and measurable personal and institutional “value,” and data entry, where possible, should be carried out by direct electronic health record–related data capture to avoid duplication of efforts” [61]. Perhaps, a more meaningful accreditation for brachytherapists needs to be revisited.

If brachytherapy is to survive as the most conformal radiation delivery method for cervical cancer with the best patient outcomes to date, it is incumbent upon radiation oncology training programs to re-prioritize brachytherapy training, since offering focused training after residency completion will remain a challenge. While the value of IMRT, SBRT, and other specialized forms of external beam radiation are recognized, none of these systems can compare to the dose escalation or dosimetric properties of a gynecologic implant and evidence has demonstrated a reduction in cervical cancer cure rates if attempts are made to substitute them for brachytherapy. Alternative methods such as simulation to help teach brachytherapy techniques should be examined and studied in the future.

8. Impact of timeliness of radiation therapy on treatment outcome

Numerous studies have examined the impact of treatment duration, and suggest that timely completion of external beam radiation and brachytherapy is a critical factor affecting local tumor control and overall survival in patients with loco-regional cervical cancer treated for curative intent. Despite the potential interrelation of radiation treatment duration and confounding factors related to tumor anatomy, tumor biology, and tumor response, it has been well accepted that unnecessary delays and breaks in radiation therapy should be avoided. Treatment including both EBRT and brachytherapy should be completed within 56–63 days based upon retrospective and prospective studies.

In the pre-chemotherapy era, Perez and colleagues retrospectively analyzed the relationship between outcome and overall treatment time and time of intracavitary insertions in 1224 patients with advanced cervical cancer. Prolongation of treatment time to more than 7 weeks resulted in decreased pelvic tumor control rates of 0.85% per day. [62]. Similarly, Petereit et al. demonstrated in a cohort of 209 cervical cancer patients undergoing primary radiation therapy that each additional day of treatment delay beyond 55 days was associated with a 0.7% loss of pelvic tumor control and a 0.6% reduction in survival [63]. In the setting of chemoradiation for cervical cancer, some authors have suggested that treatment delay had no adverse impact on treatment efficacy [64]. However, even with chemoradiation for clinically staged locoregional cervical cancer, the preponderance of evidence suggests a similar inverse relationship of treatment duration and outcome, both in terms of local tumor control and survival [65–68], with the cumulative evidence suggesting that treatment should be completed within seven to nine weeks.

In summary, while randomized controlled data are not available to identify the optimal treatment duration for patients undergoing chemo-radiotherapy and brachytherapy, every effort should be made complete the overall treatment in less than 56 to 63 days.

9. Initiation of brachytherapy during EBRT

Timing of initiation of brachytherapy in locally advanced cervical cancer is variable. Clinical decision to initiate brachytherapy is usually driven by several tumor characteristics such as pretreatment tumor volume and on treatment response to the fractionated EBRT. Both of these factors are known to be indicative of post-treatment local control and long-term survival [69–71]. Tumor shrinkage occurs during fractionated radiotherapy and is regulated by radiation induced cellular damage, repopulation of viable cells and clearance of dead cells. Frequently, HDR brachytherapy is initiated 3–4 weeks into EBRT. In some cases additional tumor shrinkage during EBRT may be beneficial and brachytherapy initiation is delayed until the end of external beam therapy, particularly for locally advanced cervical cancer where a smaller tumor volume may simplify and improve efficacy of brachytherapy.

LDR and HDR brachytherapy have variable treatment schedules and utilize different isotope sources. Questions whether HDR or LDR improve results for patients with cervical cancer in terms of local control rates, survival and complications related to treatment were addressed in a 2010 Cochrane database review by Wang et al. of randomized

controlled trials (RCTs) and quasi-RCTs that compared EBRT with HDR or LDR brachytherapy for patients with locally advanced cervical cancer [72]. This was updated in 2014 by Liu et al. who did not find any differences in terms of OS, local control or treatment complications in patients who received HDR vs LDR brachytherapy [73].

Most fractionation schemes are sequenced by practicalities and resource constraints. Fewer insertions are associated with less anesthesia, less chance for operative complications, less demand for operating room time, shorter overall treatment time, with the potential for less repeat imaging and lower use of treatment planning resources. The potential disadvantages of fewer insertions include requirements for inpatient care, prolonged patient immobility and its attendant risks (if the patient is inpatient and immobilized after insertion but between fractions), and uncertainty associated with applying a single treatment plan for multiple fractions.

Finally, interstitial and intracavitary brachytherapy have not been compared using similar fractionation schedules; however, slightly lower doses are recommended by the ABS, when treating larger volumes as is often the case with interstitial brachytherapy [69].

10. Radiation treatment at multiple centers for EBRT and brachytherapy

Certain centers may not have adequate experience to routinely perform brachytherapy. Rather than forgoing brachytherapy, patients may benefit from referral to a subspecialty care center for their brachytherapy. Large studies of the effect of coordination of care on treatment delay and outcomes of patients with locally advanced cervical cancer have not been conducted. However, examining NCDB data of 15,194 patients with locoregionally advanced cervical cancer, Robin et al. demonstrated that patients who received radiation treatment split between multiple centers had similar OS compared to patients who received radiation at one center (HR 1.043, CI 0.960–1.132) [37]. In the same study, neither treatment setting (urban versus rural) nor distance to the hospital (<25 vs. >25 miles) was significantly associated with receiving EBRT plus brachytherapy with concomitant chemotherapy.

Showalter et al. conducted an observational cohort study of 1048 patients with locoregionally advanced cervical cancer to evaluate the influence of tumor-related, demographic, and geospatial factors on the receipt of quality cervical cancer care [56]. The authors found that neither distance to treatment facility or high-volume treatment facility, nor patient residence in a metropolitan, urban or suburban county was associated with the receipt of brachytherapy. Living within 3.5 miles of a high-volume center was associated with unexpectedly lower likelihood of receiving high quality care. Therefore, distance to a high volume center was not a predictor of receiving quality care. The referral patterns and coordination of care to assure treatment at a high-volume center seem to be more important than distance alone.

11. Multidisciplinary coordination of care

The many interdependent aspects of chemo-radiation treatment require close collaboration between gynecologic oncology and radiation oncology. Completing treatment within 8–9 weeks, preferably 7 weeks and avoiding treatment delays, is one of the most consistent and important prognostic factors for women with cervical cancer [63]. This requires that brachytherapy is initiated within a timely fashion after or during chemo-radiation. Low dose rate (LDR) brachytherapy is typically delivered within a few days of completing the 5-week course of radiation and then repeated 10–14 days later [11]. HDR brachytherapy requires that up to 6 insertions are performed in the same time frame so treatment can be initiated after completing external beam and delivered twice a week or started earlier during external beam. To ensure that adequate dose can be delivered to the cervix, it is preferable that the tumor regress to less than 4 cm. Chemotherapy should be delivered concurrently with radiation therapy. Most commonly treatment is

delivered with weekly cisplatin at 40 mg/m², which is started in the first week of treatment and continued while EBRT is being delivered.

To coordinate each of these aspects of treatment, close ongoing collaboration among physicians (gynecologic, radiation and medical oncologists), as well as other staff is imperative to ensure smooth and timely initiation and completion of the treatment plan.

The multidisciplinary team should develop a plan for the following:

1. Date of radiation start. Chemotherapy should be coordinated to start within 5 days. Ideally radiation and cisplatin start coordinated on a Monday or a Tuesday.
2. Dates for subsequent cycles of chemotherapy and how often patients will be seen by their oncologist for chemotherapy clearance. Labs are typically checked weekly.
3. Plan for brachytherapy including where and when it will be performed.
4. Consideration for the presence of the gynecologic oncologist at brachytherapy. In some practices, the gynecologic oncologist is present at the first fraction to place a Smit sleeve.
5. Dates and types of repeat imaging. MRI prior to or with brachytherapy is often used to plan brachytherapy for at least the initial fraction.
6. Plan to manage hematologic toxicity, including transfusion and growth factor support for neutropenia. Filgrastim may be indicated to ensure that adequate absolute neutrophil count (ANC) prior to brachytherapy procedure.
7. Ensure insurance authorizations are obtained for both, EBRT and brachytherapy to facilitate uninterrupted radiation treatment completion within 56–63 days.

In some cases, external beam radiation is delivered closer to home while brachytherapy is delivered at a referral center. This approach has the advantage of having the most experienced physician perform brachytherapy but requires additional coordination between external beam radiation oncologist and brachytherapist. Additional issues that should be discussed

1. Date that patient starts and completes EBRT
2. Anticipated dates of brachytherapy
3. Which physician will plan and deliver boosts and how brachytherapy doses may impact lymph node or parametrial boosts.

12. Patient navigation

Patient Navigation has been most studied in breast cancer. The concept of patient navigation (PN) was developed as a strategy to reduce breast cancer treatment-related disparities and improve outcomes by addressing barriers to cancer care. Once PN was implemented, the 5-year survival for breast cancer in the targeted population increased from 39% to 79% [74].

Cervical cancer disproportionately affects underserved populations with 30–50% higher mortality rates in groups such as the American Indians and others [75]. For these vulnerable populations, PN programs have improved and demonstrated cost effectiveness for both cervical cancer screening rates and timely completion of chemo-radiation treatment [76,77]. In addition, a dedicated PN program demonstrated a reduction in overall treatment time in underserved patient populations including American Indians and Latinas with cervical cancer [78,79].

Dedicated PN for cervical cancer patients may play a critical role due to the complexity of treatment – especially if patients receive external beam radiation and chemotherapy in the community and are referred to another facility with brachytherapy expertise. Active PN for these patients may lead to completion of all treatments within the guideline of 56–63 days that invariably will improve survival and patient satisfaction rates.

13. Summary

In summation, brachytherapy is well established as integral component in the standard of care for treatment of patients receiving primary radiotherapy for cervical cancer.

Research has shown a disturbingly high recent decline in the utilization of brachytherapy, which has been coupled with increased mortality risk. SGO and ABS concur with National Comprehensive Cancer Network (NCCN) guidelines that conformal external beam therapies such as IMRT or SBRT should not be used as alternatives to brachytherapy in patients undergoing primary curative-intent radiation therapy for cervical cancer.

Furthermore, computed tomography (CT) or magnetic resonance imaging (MRI)-based image-guided adaptive brachytherapy is evolving as the preferred brachytherapy method with improved tumor coverage while sparing surrounding tissues. With careful care coordination EBRT and brachytherapy can be successfully delivered at different treatment centers without compromising treatment time and outcome in areas where access to brachytherapy maybe limited. All efforts to include brachytherapy in the radiation treatment of cervical cancer with timely completion of chemo-radiation and brachytherapy should be made.

Conflict of interest statement

Dr. Catheryn Yashar served on the Advisory Board of Cianna Medical and MicroChips. All other co-authors have no conflicts of interest to declare.

Author contributions

All authors were involved in the writing, revision, and approved the final manuscript.

References

- [1] GLOBOCAN, (IARC). Cervical cancer: estimated incidence, mortality and prevalence worldwide in 2012. Section of cancer surveillance (21/1/2018), <http://globocan.iarc.fr/old/FactSheets/cancers/cervix-new.asp> 2012.
- [2] Radical hysterectomy, Medscape, WebMD, Jan 16, 2013, (Retrieved 22 March 2014).
- [3] K. Hellman, A.C. Hellström, B.F. Pettersson, Uterine cervix cancer treatment at Radiumhemmet: 90 years' experience. Time trends of age, stage, and histopathology distribution, *Cancer Med.* 3 (2014) 284–292.
- [4] R. Abbe, The use of radium in malignant disease, *Lancet* 2 (1913) 524–527.
- [5] R.F. Mould, The historical roots of modern brachytherapy for cervical and endometrial cancer, in: E.W. Vahrson (Ed.), *Radiation Oncology of Gynecologic Cancers*, Springer-Verlag, Berlin, Heidelberg, 1997.
- [6] G.H. Fletcher, et al., A physical approach to the design of applicators in radium therapy of cancer of the cervix uteri, *Am. J. Roentgenol.* 60 (1952) 77–84.
- [7] R.M. Lanciano, M. Won, L.R. Coia, et al., Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: a final report of the 1973 and 1978 patterns of care studies, *Int. J. Radiat. Oncol. Biol. Phys.* 20 (1991) 667–676.
- [8] M. Morris, P.J. Eifel, J. Lu, P.W. Grigsby, et al., Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer, *N. Engl. J. Med.* 340 (1999) 1137–1143.
- [9] P.G. Rose, B.N. Bundy, E.B. Watkins, et al., Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer, *N. Engl. J. Med.* 340 (1999) 1144–1153.
- [10] C.W. Whitney, W. Sause, B.N. Bundy, et al., Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB–IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study, *J. Clin. Oncol.* 17 (1999) 1339–1348.
- [11] P.J. Eifel, K. Winter, M. Morris, et al., Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01, *J. Clin. Oncol.* 22 (2004) 872–880.
- [12] P.G. Rose, S. Ali, E. Watkins, J.T. Thigpen, et al., Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study, *J. Clin. Oncol.* 25 (2007) 2804–2810.
- [13] P.J. Eifel, W.W. Thoms Jr., T.L. Smith, et al., The relationship between brachytherapy dose and outcome in patients with bulky endocervical tumors treated with radiation alone, *Int. J. Radiat. Oncol. Biol. Phys.* 28 (1994) 113–118.
- [14] A.N. Viswanathan, R. Cormack, B. Rawal, et al., Increasing brachytherapy dose predicts survival for interstitial and tandem-based radiation for stage IIIB cervical cancer, *Int. J. Gynecol. Cancer* 19 (2009) 1402–1406.

- [15] K. Tanderup, P.J. Eifel, C.M. Yashar, et al., Curative radiation therapy for locally advanced cervical cancer: brachytherapy is NOT optional, *Int. J. Radiat. Oncol. Biol. Phys.* 88 (2014) 537–539.
- [16] M.D. Logsdon, P.J. Eifel, FIGO IIB 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.* 43 (1999) 763–775.
- [17] J. Karlsson, A.C. Dreifaldt, L.B. Mordhorst, B. Sorbe, Differences in outcome for cervical cancer patients treated with or without brachytherapy, *Brachytherapy* 16 (2017) 133–140.
- [18] A.N. Viswanathan, S. Beriwal, J.F. De Los Santos, et al., American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy, *Brachytherapy* 11 (2012) 47–52.
- [19] NCCN, Clinical practice guidelines in oncology. Cervical cancer. Version 1.2018, https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf.
- [20] ICRU report 38, Dose and Volume Specification for Reporting Intracavitary Therapy in Gynecology, International Commission on Radiation Units and Measurements, Bethesda, MD, 1985 1–20.
- [21] ICRU report 89, Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix, International Commission on Radiation Units and Measurements, Bethesda, MD, 2016 1–274.
- [22] R. Mazon, P. Castelnau-Marchand, et al., Tumor dose-volume response in image-guided adaptive brachytherapy for cervical cancer: a meta-regression analysis, *Brachytherapy* 15 (2016) 537–542.
- [23] P. Castelnau-Marchand, C. Chargari, C. Haie-Meder, et al., Image-guided adaptive brachytherapy in locally advanced cervical cancer: recent advances and perspectives, *Curr. Opin. Oncol.* 28 (2016) 419–428.
- [24] A. Sturza, R. Pötter, L.U. Fokdal, et al., Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study, *Radiother. Oncol.* 120 (2016) 428–433.
- [25] C. Vale, J.F. Tierney, L.A. Stewart, Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, *J. Clin. Oncol.* 26 (2008) 5802–5812.
- [26] C. Charra-Brunaud, V. Harter, M. Delannes, et al., Impact of 3D image-based PDR brachytherapy on prospective of patients treated for cervix carcinoma in France: results of the French STIC prospective study, *Radiother. Oncol.* 103 (2012) 305–313.
- [27] R. Mazon, L.U. Fokdal, K. Kirchheiner, et al., Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: results from the prospective multicenter EMBRACE study, *Radiother. Oncol.* 120 (2016) 412–419.
- [28] S.C. Kamran, M.M. Manuel, L.P. Cho, et al., Comparison of outcomes for MR-guided versus CT-guided high-dose-rate interstitial brachytherapy in women with locally advanced carcinoma of the cervix, *Gynecol. Oncol.* 145 (2017) 284–290.
- [29] J.C. Dimopoulos, P. Petrow, K. Tanderup, et al., Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy, *Radiother. Oncol.* 103 (2012) 113–122.
- [30] M.J. Zelefsky, Z. Fuks, M. Hunt, et al., High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients, *Int. J. Radiat. Oncol. Biol. Phys.* 53 (2002) 1111–1116.
- [31] P.A. Kupelian, C.A. Reddy, T.P. Carlson, et al., Preliminary observations on biochemical relapse-free survival rates after short-course intensity-modulated radiotherapy for localized prostate cancer, *Int. J. Radiat. Oncol. Biol. Phys.* 53 (2002) 904–912.
- [32] L.K. Mell, A.K. Mehrotra, A.J. Mundt, Intensity-modulated radiation therapy use in the US, 2004, *Cancer* 104 (2005) 1296–1303.
- [33] P.J. Eifel, J. Moughan, B. Erickson, et al., Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: a patterns of care study, *Int. J. Radiat. Oncol. Biol. Phys.* 60 (2004) 1144–1153.
- [34] K. Han, M. Milosevic, A. Fyles, et al., Trends in the utilization of brachytherapy in cervical cancer in the United States, *Int. J. Radiat. Oncol. Biol. Phys.* 87 (2013) 111–119.
- [35] P.J. Eifel, A. Ho, N. Khalid, et al., Patterns of radiation therapy practice for patients treated for intact cervical cancer in 2005 to 2007: a quality research in radiation oncology study, *Int. J. Radiat. Oncol. Biol. Phys.* 89 (2014) 249–256.
- [36] B.S. Gill, J.F. Lin, T.C. Krivak, et al., National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements, *Int. J. Radiat. Oncol. Biol. Phys.* 90 (2014) 1083–1090.
- [37] T.P. Robin, A. Amini, T.E. Scheffer, et al., Disparities in standard of care treatment and associated survival decrement in patients with locally advanced cervical cancer, *Gynecol. Oncol.* 143 (2016) 319–325.
- [38] Commission on Cancer, Cancer Program Practice Profile Report (CP3R), 2015 (data released on October 23, 2017).
- [39] E.P. Saibishkumar, F.D. Patel, S.C. Sharma, et al., Results of external-beam radiotherapy alone in invasive cancer of the uterine cervix: a retrospective analysis, *Clin. Oncol. (R. Coll. Radiol.)* 18 (2006) 46–51.
- [40] R.A. Sethi, G. Jozsef, D. Grew, et al., Is there a role for an external beam boost in cervical cancer radiotherapy? *Front. Oncol.* 30 (2013) 3:3.
- [41] M. Cengiz, A. Dogan, G. Ozyigit, et al., Comparison of intracavitary brachytherapy and stereotactic body radiotherapy dose distribution for cervical cancer, *Brachytherapy* 11 (2012) 125–129.
- [42] C.A. Mantz, F. Abu Shahin, S. Sandadi, et al., Stereotactic body radiation therapy as a boost alternative to brachytherapy for primary gynecologic cancer: disease control and quality of life outcomes from a phase II trial, *Int. J. Radiat. Oncol. Biol. Phys.* 93 (2015) S202.
- [43] C.H. Hsieh, H.J. Tien, S.M. Hsiao, et al., Stereotactic body radiation therapy via helical tomotherapy to replace brachytherapy for brachytherapy-unsuitable cervical cancer patients - a preliminary result, *Onco Targets Ther.* 6 (2013) 59–66.
- [44] M. Mollà, L. Escude, P. Nouet, et al., Fractionated stereotactic radiotherapy boost for gynecologic tumors: an alternative to brachytherapy? *Int. J. Radiat. Oncol. Biol. Phys.* 62 (2005) 118–124.
- [45] G.J. Kubicek, J. Xue, Q. Xu, et al., Stereotactic body radiotherapy as an alternative to brachytherapy in gynecologic cancer, *Biomed. Res. Int.* 2013 (2013) 898953.
- [46] S. Marnitz, C. Köhler, V. Budach, et al., Brachytherapy-emulating robotic radiosurgery in patients with cervical carcinoma, *Radiat. Oncol.* 8 (2013) 109.
- [47] J.A. Haas, M.R. Witten, O. Clancey, et al., CyberKnife boost for patients with cervical cancer unable to undergo brachytherapy, *Front. Oncol.* 2 (2012) 25.
- [48] A. Maerker, M. Schützwohl, Erfassung von psychischen Belastungsfolgen: Die Impact of Event Skala-revidierte Version (IES-R), *Diagnostica* 44 (1998) 130–141.
- [49] D. Georg, C. Kirisits, M. Hillbrand, et al., Image-guided radiotherapy for cervix cancer: high-tech external beam therapy versus high-tech brachytherapy, *Int. J. Radiat. Oncol. Biol. Phys.* 71 (2008) 1272–1278.
- [50] B. Otahal, M. Dolezel, J. Cvek, et al., Dosimetric comparison of MRI-based HDR brachytherapy and stereotactic radiotherapy in patients with advanced cervical cancer: a virtual brachytherapy study, *Rep. Pract. Oncol. Radiother.* 19 (2014) 399–404.
- [51] J.J. Compton, L.E. Gaspar, D.C. Shrieve, et al., Resident-reported brachytherapy experience in ACGME-accredited radiation oncology training programs, *Brachytherapy* 12 (2013) 622–627.
- [52] G.E. Hanks, D.F. Herring, S. Kramer, Patterns of care outcome studies. Results of the national practice in cancer of the cervix, *Cancer* 51 (1983) 959–967.
- [53] B.W. Corn, A.L. Hanlon, T.F. Pajak, et al., Technically accurate intracavitary insertions improve pelvic control and survival among patients with locally advanced carcinoma of the uterine cervix, *Gynecol. Oncol.* 53 (1994) 294–300.
- [54] M.S. Lee, S.J. Tsai, C.C. Lee, et al., Higher caseload improves cervical cancer survival in patients treated with brachytherapy, *Radiat. Oncol.* 9 (2014) 234.
- [55] G.L. Smith, J. Jiang, S.H. Giordano, et al., Trends in the quality of treatment for patients with intact cervical cancer in the United States, 1999 through 2011, *Int. J. Radiat. Oncol. Biol. Phys.* 92 (2015) 260–267.
- [56] T.N. Showalter, F. Camacho, L.A. Cantrell, et al., Determinants of quality care and mortality for patients with locally advanced cervical cancer in Virginia, *Medicine (Baltimore)* 95 (2016) e2913.
- [57] J. Rose, P.Y. McLaughlin, C.B. Falkson, Brachytherapy practice across Canada: a survey of workforce and barriers, *Brachytherapy* 12 (2013) 615–621.
- [58] D.G. Peterit, S.J. Frank, A.N. Viswanathan, et al., Brachytherapy: where has it gone? *J. Clin. Oncol.* 33 (2015) 980–982.
- [59] R. Pötter, P. Georg, J.C. Dimopoulos, 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.* 100 (2011) 116–123.
- [60] S. Grover, M.M. Harkenrider, L.P. Cho, et al., Image guided cervical brachytherapy: 2014 survey of the American Brachytherapy Society, *Int. J. Radiat. Oncol. Biol. Phys.* 94 (2016) 598–604.
- [61] P.E. Wallner, P. Kupelian, B. Erickson, et al., The American Board of Radiology Focused Practice Recognition in Brachytherapy (FPRB) Program: opportunities lost, lessons learned, and future implications, *Pract. Radiat. Oncol.* 5 (2015) 427–432.
- [62] C.A. Perez, P.W. Grigsby, H. Castro-Vita, et al., Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy, *Int. J. Radiat. Oncol. Biol. Phys.* 32 (1995) 1275–1288.
- [63] D.G. Peterit, J.N. Sarkaria, R. Chappell, et al., The adverse effect of treatment prolongation in cervical carcinoma, *Int. J. Radiat. Oncol. Biol. Phys.* 32 (1995) 1301–1307.
- [64] N. Shaverdian, V. Gondi, K.L. Sklenar, et al., Effects of treatment duration during concomitant chemoradiation therapy for cervical cancer, *Int. J. Radiat. Oncol. Biol. Phys.* 86 (2013) 562–568.
- [65] S. Song, S. Rudra, M.D. Hasselle, et al., The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy, *Cancer* 119 (2013) 325–331.
- [66] B.J. Monk, C. Tian, P.G. Rose, et al., Which clinical/pathologic factors matter in the era of chemoradiation as treatment for locally advanced cervical carcinoma? Analysis of two Gynecologic Oncology Group (GOG) trials, *Gynecol. Oncol.* 105 (2007) 427–433.
- [67] M. Amneus, S. Park, L. Delic, et al., Survival impact of prolonged treatment duration in primary chemoradiation for cervical cancer, *Obstet. Gynecol. Int. J.* 3 (2015), 00081.
- [68] D.B. Manders, A. Morón, D. McIntire, et al., Locally advanced cervical cancer: outcomes with variable adherence to treatment, *Am. J. Clin. Oncol.* 2 (2016 Jun) (Epub ahead of print).
- [69] J.Z. Wang, N.A. Mayr, D. Zhang, 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* 116 (2010) 5093–5101.
- [70] T.K. Sethi, N.K. Bhalla, A.N. Jeeva, S. Rawat, R. Oberoi, Magnetic resonance imaging in carcinoma cervix - does it have a prognostic relevance, *J. Can. Res. Ther.* 1 (2005) 103–107.
- [71] J.J. Kovalic, C.A. Perez, P.W. Grigsby, The effect of volume of disease in patients with carcinoma of the uterine cervix, *Int. J. Radiat. Oncol. Biol. Phys.* 21 (1991) 905–910.
- [72] X. Wang, et al., High dose rate versus low dose rate intracavitary brachytherapy for locally advanced uterine cervix cancer, *Cochrane Database Syst. Rev.* 2010 (7) (2010) CD007563.
- [73] R. Liu, X. Wang, J.H. Tian, et al., High dose rate versus low dose rate intracavitary brachytherapy for locally advanced uterine cervix cancer, *Cochrane Database Syst. Rev.* 10 (2014) CD007563.
- [74] H.P. Freeman, Patient navigation: a community based strategy to reduce cancer disparities, *J. Urban Health Bull. N. Y. Acad. Med.* 83 (2006) 139–141.

- [75] P.R. Band, R.P. Gallagher, W.J. Threlfall, et al., Rate of death from cervical cancer among native Indian women in British Columbia, *CMAJ* 147 (1992) 1802–1804.
- [76] S. Percac-Lima, J.M. Ashburner, A.H. Zai, et al., Patient navigation for comprehensive cancer screening in high-risk patients using a population-based health information technology system: a randomized clinical trial, *JAMA Intern. Med.* 176 (2016) 930–937.
- [77] K. Dessources, E. Pineda, M. Amneus, C.H. Holschneider, The cost-effectiveness of cancer care navigation in patients with locoregional cervical cancer undergoing primary chemoradiation, *Gynecol. Oncol.* 145 (S1) (2017) 71.
- [78] B.A. Guadagnolo, A. Boylan, M. Sargent, et al., Patient navigation for American Indians undergoing cancer treatment: utilization and impact on care delivery in a regional health care center, *Cancer* 117 (2011) 2754–2761.
- [79] M.W. Amneus, L.M. Garcia, E. Pineda, C.H. Holschneider, Improving quality of care with cervical cancer patient navigation, *Gynecol. Oncol.* 133 (S1) (2014) 34.