



Interstitial Brachytherapy for Locally Advanced Cervical Cancer

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Abstract

Purpose: To report institutional outcomes for the use of interstitial brachytherapy for locally advanced cervical cancer.

Methods and Materials: Retrospective analysis was performed on patients treated for cervical cancer at the Ohio State University Wexner Medical Center from 2000 to 2014. A total of 525 patients were identified and 52 of these patients received interstitial brachytherapy and were included in the analysis. All patients received external beam radiation. All patients were treated with low-dose-rate interstitial brachytherapy, except for one patient who was treated with high-dose-rate interstitial brachytherapy. Actuarial estimates of disease free survival, locoregional failure free survival (LRFSS), distant metastasis free survival, and overall survival were calculated by Kaplan-Meier.

Results: At a median OS of 22.1 months for all 52 patients treated with interstitial brachytherapy, LRFSS was 70% at 1 year, 67% at 2 years, and 61% at 3 years. Disease free survival at 1, 2, and 3 years were 61%, 52%, and 45%, respectively. Distant metastasis free survival was 81%, 69%, and 65% at 1, 2, and 3 years, respectively. Overall survival was 67% at 1 year, 47% at 2 years, and 30% at 3 years. The grade 3 toxicity rate was 9.6% but no grade 4 or higher toxicity occurred.

Conclusion: Interstitial brachytherapy provides good local control for patients with locally advanced cervical cancer with acceptable toxicity. However, local and distant failures are still occurring despite this treatment.

treatment for locally advanced cervical cancer [4-8]. Today, standard treatment of locally advanced cervical carcinoma include external beam radiation therapy (EBRT), concurrent cisplatin containing chemotherapy, and a brachytherapy boost to the cervix to total doses between > 80 - 90 Gy to maximize outcomes [9].

As a means of radiation dose escalation to tumor with normal tissue sparing, brachytherapy is critical to the curative management of cervical cancer. When executed correctly and in conjunction with EBRT it results in improved survival rates [10-13]. The majority of patients with cervical cancer are able to be treated with intracavitary brachytherapy. However, patients with more advanced cervical cancers may require interstitial brachytherapy. Interstitial brachytherapy is most commonly used for cervical cancers with distal vaginal involvement, bulky tumors with poor response to pelvic radiation, vaginal stenosis which does not permit intracavitary treatment, and in recurrent disease [14,15]. Because less than 10% of women with cervical cancer are treated with interstitial brachytherapy [16], there is little data on patient outcomes following treatment. The primary aim of this study is to report locoregional failure free survival (LRFSS) in patients treated with interstitial brachytherapy as part of their definitive chemoradiation for cervical cancer. Secondary aims are to report disease progression-free survival (DFS), distant metastasis free survival (DMFS) and overall survival (OS) rates.

Methods

This retrospective cohort study was designed to evaluate clinical outcomes in patients diagnosed with locally advanced cervical carcinoma treated with definitive RT and concurrent cisplatin and interstitial brachytherapy per institutional guidelines. With approval of the Institutional Review Board, clinical data were abstracted from the medical and radiotherapy records. Study inclusion required a diagnosis of cervical cancer, with histologies including adenocarcinoma, and squamous and adenosquamous carcinomas, treated with concurrent chemoradiation therapy plus interstitial brachytherapy from January 2000 to December 2014. All pathology was reviewed at Ohio State University Wexner Medical Center (OSUWMC). All patients had their brachytherapy performed at OSUWMC and were at least 18 years of age at diagnosis. Patients treated with primary surgical intervention or those with recurrent disease were excluded.

Introduction

Cervical cancer is the third most common gynecologic cancer in United States of America (USA) and in 2013 approximately 12,000 new cases of cervical cancer were diagnosed in this country [1]. Historically, local control rates after definitive radiation therapy (RT) have ranged between 65% and 95% for stage IB, 72 - 82% for stage IIB, and 50 - 83% for stage III [2], according to the International Federation of Gynecology and Obstetrics (FIGO) system [3]. 10 year disease free survival was approximately 82% for stage IB, 65% for stage IIB, and 40% for stage III [2]. In 1999, after results of 5 randomized clinical trials demonstrating improved survival rates with the addition of chemotherapy, the National Cancer Institute declared concurrent platinum based chemoradiation as standard

Citation: Denlinger N, Nolan N, Bixel K, Salani R, Martin D, et al. (2015) Interstitial Brachytherapy for Locally Advanced Cervical Cancer. Int J Womens Health Wellness 1:003

Received: September 16, 2015; **Accepted:** October 19, 2015; **Published:** October 21, 2015

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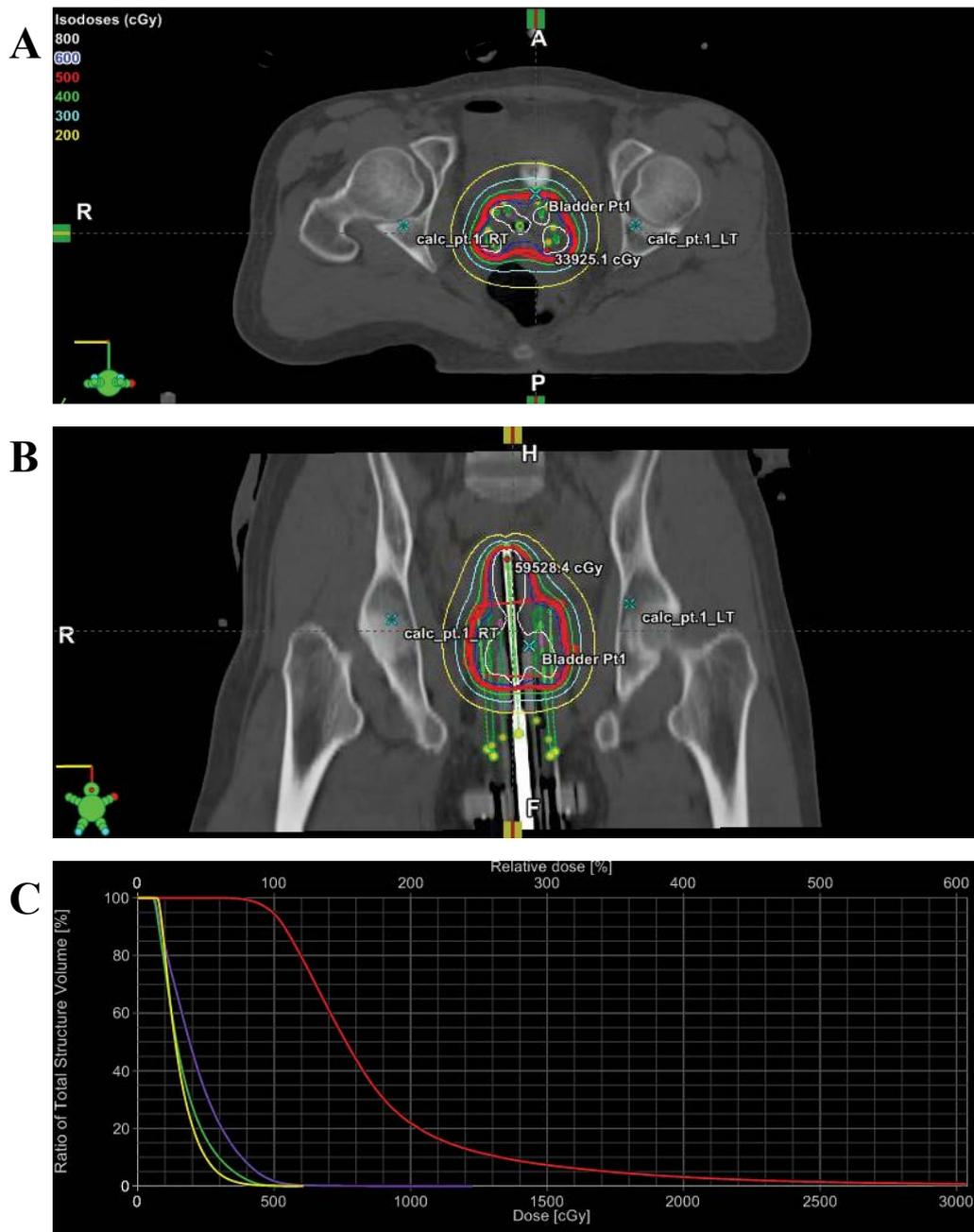


Figure 1: CT based treatment plan in (A) axial and (B) coronal planes for a patient with FIGO Stage IVA cervical cancer treated with HDR interstitial brachytherapy. Dose Volume Histogram (C) demonstrating dose to the CTV (red line) and dose to bladder (purple line), rectum (green line), and sigmoid (yellow line).

A search of the clinical databases at The James Cancer Hospital of the OSUWMC was performed and identified 525 patients diagnosed with cervical carcinoma seen in consultation by Radiation Oncology. Retrospective chart review of these 525 patients was performed and revealed 52 patients treated with interstitial brachytherapy. Information was abstracted from the patient's medical record and includes: age, date of diagnosis, stage, tumor histology, treated areas, date of initiation of therapy, chemotherapy, dates/doses of EBRT, dates/doses of brachytherapy, response to treatment, date and location of recurrence if applicable, treatment toxicity and survival status.

Treatment protocol

All patients completed EBRT prior to brachytherapy and underwent a single interstitial implant using a Syed-Neblett template (Best Medical International, Incorporation, and Springfield, Virginia, USA). Techniques of low-dose-rate (LDR) and high-dose-rate (HDR) interstitial brachytherapy have been previously reported [17-19]. Clinical and imaging findings prior to EBRT and brachytherapy were used to estimate tumor volume and number of needles required for

implantation. While under general anesthesia, a pelvic exam was performed to evaluate extent of residual disease. A foley catheter was placed in the bladder and the balloon was filled with 7 cc dilute omnipaque. Radiopaque markers were placed in the cervix and vagina to delineate extent of disease. A tandem was placed in the uterus and a vaginal obturator was placed in the vagina. The Syed template was then secured over the obturator about 1 cm from the perineum. Needles were inserted through the Syed template to approximately 2 cm above the extent of disease under fluoroscopic guidance.

Before 2007, orthogonal films with dummy sources were obtained after needle placement was completed for treatment planning using Theraplan Plus (MDS Nordion, Ottawa, ON Canada). The dose rate was prescribed to point A or the minimal peripheral dose. In 2007, computed tomography (CT) based planning was implemented and was performed after needle implantation under fluoroscopic guidance. Needle positions were adjusted if necessary and repeat CT images were obtained until final needle location was determined. The clinical target volume (CTV) was contoured on the CT images based on pre and post-treatment clinical and imaging findings. The

dose was prescribed to the CTV such that at minimum 90% of the CTV (D90) received the prescription dose and with acceptable OARs doses (Figure 1). The goal was to achieve a total D90 of 80 - 85 Gy to the CTV with a total dose to 2 cc (D_{2cc}) of the rectum and sigmoid less than 75 Gy and bladder less than 90 Gy. Treatment planning was performed in BrachyVision (Varian Medical Systems, Incorporation, Palo Alto, California, USA) to manually optimize CTV coverage with acceptable dose to OARs. All but one patient were treated with LDR brachytherapy. For the patients treated with LDR brachytherapy, Cesium-137 sources were placed in the central tandem and Iridium-192 sources were loaded into the interstitial needles on the day of the implant and left in place for the duration of the treatment. After 2013, patients were treated with HDR brachytherapy with a single implant with twice daily treatments for a total of 3 - 5 fractions. Treatment was delivered via the VariSource HDR remote after loader (Varian Medical Systems, Incorporation, Palo Alto, California, USA) using Iridium-192.

Clinical and treatment characteristics at diagnosis

Baseline clinical characteristics for the 52 patients are summarized in table 1. All patients were staged according to the 2009 FIGO staging system [3]. Treatment characteristics are summarized in table 2. All patients received EBRT and all but one patient had concurrent chemotherapy containing cisplatin. EBRT median dose was 45 Gy (range 39.6 - 45). Four patients treated at outside facilities with EBRT did not have data from pelvic radiation dose available. Four patients were treated using intensity modulated radiation therapy; all others were treated with 3 dimensional (3D) conformal treatment planning. Eleven patients received a parametrial boost (range, 5.4 - 16 Gy). One patient initially received emergency EBRT for vaginal bleeding, then pelvic and para-aortic lymph node dissection followed by EBRT to 25 Gy. Interstitial LDR brachytherapy median dose was 40 Gy (range, 30 - 45).

The indication for interstitial brachytherapy was bulky disease in 24 patients, extensive vaginal involvement in 7 patients, and poor anatomy/vaginal stenosis in 21 patients. A central tandem was placed in all patients and the average number of interstitial needles was 12 (range from 6 - 30). Three patients had an initial intracavitary treatment but were converted to interstitial brachytherapy due to inadequate tumor coverage (n = 1) or poor anatomy (n = 2). One patient received HDR interstitial brachytherapy and was treated to 25 Gy in 5 fractions. CT based planning was used for 23 patients and 2 dimensional planning was used for the other 29 patients.

After completion of brachytherapy, patients were seen at one month follow-up by the treating Radiation Oncologist and then every 3 months for the first 2 years, every 6 months for 3 to 5 years, and then yearly by either Gynecology Oncology or Radiation Oncology. Treatment related complications were evaluated throughout patient follow-up and were quantified by the Common Toxicity Criteria for Adverse Events (CTCAE, version 4.03 - June 14th, 2010) [20].

Statistical analysis

Actuarial estimates of LRF, DFS, DMFS and OS were determined using the Kaplan-Meier method. Locoregional failure (LRF) was defined as disease recurrence or progression in the pelvis proven by biopsy or imaging. Distant metastasis was defined as disease recurrence or progression outside the pelvis, including para-aortic nodal recurrence, proven by biopsy or imaging subsequently. DFS was defined as the percent of patients that survived without disease recurrence or progression of disease. LRF was defined as the percent of patients that survived without LRF. DMFS was defined as the percent of patients that survived without distant metastasis. All clinical outcomes were calculated from the date of completion of treatment to the date of death or last follow-up if the patient's status at time of collection was alive or unknown.

Results

Disease free survival/distant metastasis free survival/overall survival

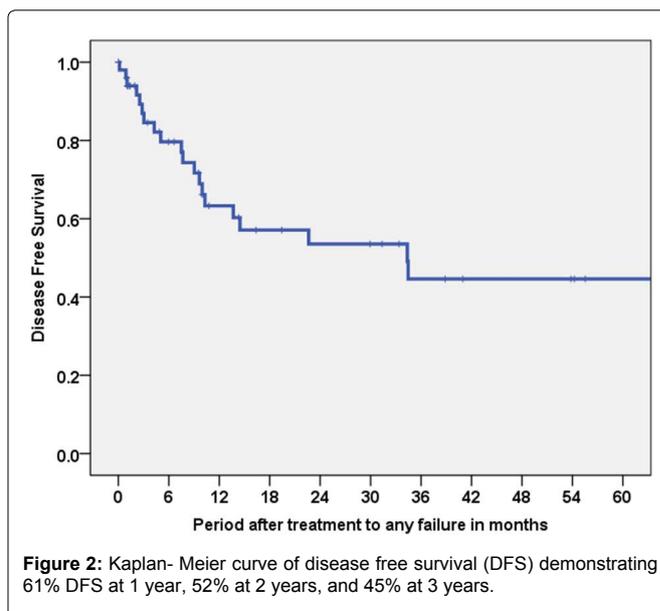
Of the 52 patients included in the study, 20 patients had recurrence

Table 1: Clinical characteristics at diagnosis table 1 - n = 52.

Age, median (range) Histology, % (n)	56 years (29-86)
Squamous Cell Carcinoma (SCC)	90 % (47)
Not characterized	40 % (19)
Well differentiated	6 % (3)
Moderately differentiated	29 % (15)
Poorly differentiated	21 % (10)
SCC with focal neuroendocrine feature	2 % (1)
SCC with sarcomatoid features	2 % (1)
Adenocarcinoma	8 % (4)
Adenosquamous Carcinoma	2 % (1)
FIGO stage at diagnosis, % (n)	
IB	2 % (1)
IB2	3 % (2)
IIA	8 % (4)
IIB	23 % (12)
IIIA	12 % (6)
IIIB	46 % (24)
IVA	6 % (3)

Table 2: Treatment characteristics with median values and ranges - n = 52.

Brachytherapy dose, median (range)	40 Gy (25-45 Gy)
LDR	40 Gy (30-45 Gy)
HDR	25 Gy (25 Gy)
EBRT dose	45 Gy (39.6-45 Gy)
Total dose, median (range)	85 Gy (70-90 Gy)
Concurrent cisplatin	N = 51



or progression of disease. Of those that recurred, 50% (n = 10) had isolated LRF, 35% (n = 7) had isolated distant failure, and 15% (n = 3) had both locoregional and distant failure. The median TTP was 7.4 months, range 0.1 - 34 months. The median DFS was 34.4 months and DFS at 1, 2, and 3 years was 61%, 52%, and 45%, respectively (Figure 2). 10 patients experienced distant recurrence with a median TTP of 9.2 months, range 1 - 34 months. DMFS at 1 year was 81%, at 2 years was 69%, and at 3 years was 65% (Figure 3). The median OS for all 52 patients was 22.1 months, range 3.2 - 163 months. OS at 1 year was 67%, at 2 years was 47%, and at 3 years was 30%, with an estimated OS at 5 years of 28% (Figure 4).

Locoregional failure free survival

Thirteen patients (25%) experienced a LRF (Figure 5). For those patients with LRF, the median time to progression (TTP) was 4.7 months, range 0.1 to 34 months. LRF at 1 year was 70%, 67% at 2 years, and 61% at 3 years. Of the 13 patients with LRF, 6 patients had failure confined to the cervix or vagina that was included in high dose volume, 4 had pelvic

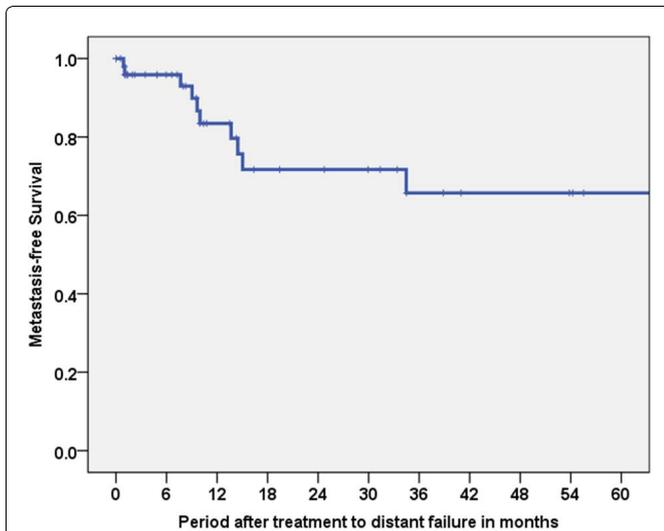


Figure 3: Kaplan- Meier curve of distant metastasis free survival (DMFS) demonstrating 81% DMFS at 1 year, 69% at 2 years, and 65% at 3 years.

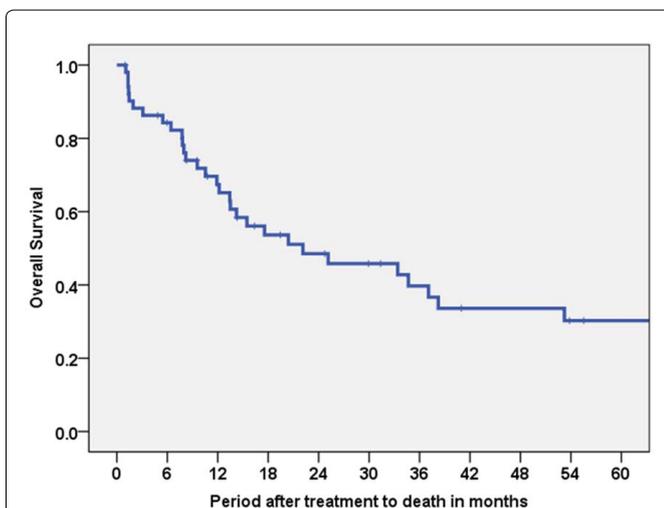


Figure 4: Kaplan- Meier curve of overall survival (OS) demonstrating 67% OS at 1 year, 47% at 2 years, and 30% at 3 years.

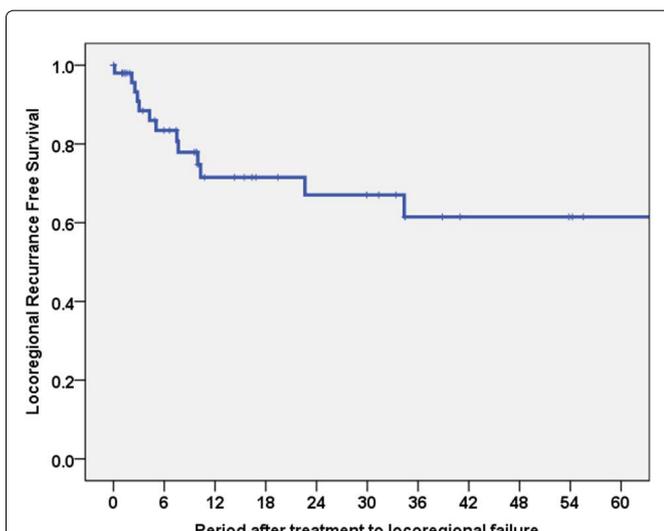


Figure 5: Kaplan- Meier curve of loco regional recurrence free survival (LRRFS) demonstrating 70% LRRFS at 1 year, 67% at 2 years, and 61% at 3 years.

recurrence outside the brachytherapy volume, and three had both local failure in pelvic lymph nodes and distant failure in the para-aortic nodes. One patient who had a local recurrence did not complete her entire

brachytherapy treatment. She suffered from acute mental status changes while in the hospital during her treatment and displaced her implant after 31 of 67 planned hours. She then received 3 additional HDR treatments using tandem and cylinder applicators and bilateral parametrial boost. MRI 3 months after treatment showed persistent/recurrent disease in cervix and left parametria, which was outside volume of tandem and cylinder treatments. Two patients classified as a local regional failure likely had persistent disease as opposed to true recurrence. One of these patients had progressive disease during external beam radiation and had rapid recurrence/progression following brachytherapy. The second patient had persistent necrotic tumor in vaginal apex one month after brachytherapy. This patient refused staging for metastatic disease at the time of recurrence. 5 patients who failed locally were planned without CT based planning and 8 of patients who failed were planned with CT based planning.

Toxicity

The rate of grade 3 toxicity was 9.6% (5 patients) including 1 vesicovaginal fistula, 3 rectovaginal fistulas, and 1 patient with both a rectovaginal fistula and a sigmoid stricture requiring loop colostomy (CTCAE, version 4.03) [20]. 3 patients with grade 3 toxicity were planned with CT based planning and all had D_{2cc} to the rectum less than 70 Gy and to the bladder less than 90 Gy. No grade 4 complications were seen.

Discussion

For women with locally advanced cervical cancer with distal vaginal involvement or bulky disease with persistent parametrial involvement after external beam radiation, intracavitary brachytherapy may not adequately treat residual disease while respecting doses to OARs [21]. In addition, vaginal narrowing or stenosis can prevent placement of intracavitary applicators. Radiation dose escalation has been attempted through other techniques, such as intensity modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) [22-24]. However, these advanced treatments have resulted in inferior survival compared to brachytherapy. A recent review of over 7000 patients treated with definitive radiation therapy from 1998 to 2011 demonstrated a decrease utilization of brachytherapy over time with a simultaneous rise of IMRT or SBRT boost to primary disease. The patients treated with brachytherapy had a median survival of 70.9 months compared to a median of 23.8 months for those receiving and IMRT or SBRT boost. Additionally, the use of IMRT or SBRT boost over brachytherapy increased risk of death more than the lack of chemotherapy [19]. Since brachytherapy is vital to the curative treatment for cervical cancer, interstitial brachytherapy may be necessary for some women. Unfortunately, this procedure is more invasive than intracavitary brachytherapy and has potential for more treatment related toxicity. However, our results show that this treatment can provide local control for women with locally advanced cervical cancer with acceptable toxicity rates.

Although there are few studies published regarding patient outcomes with interstitial brachytherapy for locally advanced cervical cancer, our results are comparable to Kannan et al. who demonstrated 2 year local control rates of 61% with 10% grade 3 toxicity [15]. These patients were all planned with CT based planning and treated with HDR interstitial brachytherapy following EBRT and concurrent chemotherapy. At a median follow-up of 51 months, Syed et al. achieved local control rates of 73% for locally advanced cervical cancer treated with LDR interstitial brachytherapy [17]. Grade 3 or 4 toxicity was also 10%. Others, such as Pinn-Bingham et al. have demonstrated higher local control rates of 85%. They treated patients with higher pelvic dose of EBRT to 50.4 Gy and performed 2 interstitial HDR implants to a total dose of brachytherapy of 36 Gy [25].

Advanced technology is a critical component of improving cervical cancer treatment outcomes. Image guided brachytherapy using CT and magnetic resonance imaging (MRI) for treatment planning has allowed for dose escalation to tumor with sparing of OARs [26]. Real time CT guidance for interstitial gynecological brachytherapy has achieved local control rates of 83% at 2 years [14]. Results with

MRI guided intracavitary brachytherapy have yielded local control rates as high as 100% at 2 years [27]. For interstitial brachytherapy planned with MRI guidance, 3 year local control rates of 100% have been achieved by Yoshida et al. [28]. The gynecologic GEC ESTRO working group has established recommendations for MRI 3D image based treatment planning for brachytherapy for cervical cancer, including dose and volume goals for tumor coverage and constraints for OARs [29]. With their treatment planning guidelines to achieve a high risk CTV D90 above 85 Gy and limit D_{2cc} of the rectum and sigmoid to 70 - 75 Gy and bladder to 90 Gy, Pötter et al. reported local control in 95 - 100% of patients with IB-IIB cervical cancer and in 85 - 90% with more advanced disease [30].

The EMBRACE trial is a prospective observation trial for patients with FIGO Stage IB-IVA cervical cancer using image guided adaptive brachytherapy to correlate clinical outcomes with GEC ESTRO planning guidelines (<https://www.embracestudy.dk/>). In a report of vaginal toxicity of 588 patients treated on the EMBRACE protocol, 30% were treated with a combined intracavitary and interstitial technique [31]. In the report by Pötter et al. using GEC ESTRO treatment recommendations, 44% of their 156 patients had combined intracavitary and interstitial brachytherapy [30]. Based on preliminary data, this brachytherapy technique, which utilizes less resources than interstitial brachytherapy [21], is feasible and results in excellent local control with acceptable side effects [32]. For patients with persistent parametrial disease following external beam radiation, the combined interstitial and intracavitary method may be superior to intracavitary brachytherapy with an external beam parametrial boost [33]. In addition, a recent dosimetric comparison of an interstitial implant compared to a combined interstitial/intracavitary technique demonstrated comparable results [34].

The addition of concurrent chemotherapy to radiation for locally advanced cervical cancer has reduced local and distant failures and improved overall 5 year survival [35]. However, even with chemotherapy, the 5 year DFS for patients with locally advanced cervical cancers remains poor at 58%. About 44% of patients may experience distant failure, with about 27% having isolated distant failures without local progression [35]. Distant recurrences occurred in only 19% of the patients in our study, with local control maintained in all but three of these failures. In order to reduce distant spread of disease, adjuvant systemic therapy options are being investigated. The addition of gemcitabine to cisplatin based chemoradiation therapy and adjuvant gemcitabine/cisplatin for patients with Stage IIB to IV cervical cancer improved 3 year PFS survival from 65% to 74% compared to standard cisplatin based chemoradiation alone [36]. Also, the currently enrolling GOG-0274/ANZGOG0902/RTOG 1174 clinical trial is investigating the use of outback carboplatin and paclitaxel following completion of definitive cisplatin based chemoradiation to potentially improve survival for patients with locally advanced cervical cancer.

Conclusions

In conclusion, our data demonstrates that interstitial brachytherapy provides good local control for patients with locally advanced cervical cancer. Unfortunately, local recurrences can still occur despite the high doses of radiation that can be delivered with this treatment. Since the majority of our patients were planned without 3 dimensional planning and no patients had MRI for treatment planning, we hope to improve on these results with our advancing technology.

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