Technical Note

Original paper

Feasibility of outpatient hybrid brachytherapy for cervical cancer with minimal sedation: Results from a single-institutional protocol

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Abstract

Purpose: Pain control techniques during high-dose-rate hybrid intracavitary-interstitial brachytherapy (HBT) for cervical cancer vary widely, with many centers opting for general anesthesia (GA) or conscious sedation (CS). Here, we describe a single-institutional series of patients treated with HBT and ASA-defined minimal sedation, utilizing oral analgesic and anxiolytic medications in substitution for GA or CS.

Material and methods: The charts of patients who underwent HBT treatments for cervical cancer from June 2018 to May 2020 were retrospectively reviewed. Prior to HBT, all patients underwent an exam under anesthesia (EUA), and Smit sleeve placement under general anesthesia or deep sedation. Oral lorazepam and oxycodone/acetaminophen were administered between 30-90 minutes before HBT procedure for minimal sedation. HBT placement was performed on computed tomography (CT) table, with needle advancement under CT-guidance.

Results: Treatments with minimal sedation were attempted in 63 patients. A total of 244 interstitial implants with 453 needles were placed via CT-guidance. Sixty-one patients (96.8%) tolerated the procedure without any additional intervention, while two patients (3.2%) required the use of epidural anesthesia. None of the patients in the series required a transition to general anesthesia for the procedure. Bleeding, which resolved with short-term vaginal packing, occurred in 22.1% of insertions.

Conclusions: In our series, the treatment of HBT for cervical cancer with minimal sedation was feasible at a high percentage (96.8%). The ability to perform HBT without GA or CS could be a reasonable option to provide image-guided adaptive brachytherapy (IGABT) with limited resources, allowing for more widespread use. Further investigations using this technique are warranted.

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Key words: interstitial brachytherapy, image-guided brachytherapy, cervical cancer, HDR brachytherapy.

Purpose

The adoption of image-guided adaptive brachytherapy (IGABT) using intracavitary applicators has led to significant improvements in local control (LC) for patients with locally advanced cervical cancer (LACC) [1-5]. IGABT enables thorough customization of each boost fraction to optimize the therapeutic radiation doses delivered to tumors, with simultaneous reduction of doses received by normal tissues [3, 4]. Over the same timeframe, advances in the design of brachytherapy applicators have allowed for the increased utilization of 'hybrid' brachytherapy (HBT) applicators, capable of simultaneous implantation of interstitial needles, along with the traditional intracavitary tandem and ovoids or tandem and ring [5, 6]. This combined technique has been shown to be particularly useful in patients with large tumors or with extensive parametrial involvement remaining after the initial chemotherapy and external beam radiotherapy (EBRT) portion of treatment, and has been repeatedly demonstrated to improve oncologic outcomes [3-8].

While both developments are promising for patients with LACC, the adoption of HBT has been relatively slow. Factors hypothesized for this have included lack of availability of necessary resources, concern about procedure tolerability, increased staffing needs, concerns over

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the highly-technical and labor-intensive nature of adding interstitial needles, and the requirement of general anesthesia or deep conscious sedation [9-11].

Techniques for pain management during high-dose-rate HBT procedures vary widely per institutional preference, with many centers choosing to perform the procedure under general anesthesia (GA) or conscious sedation (CS) to accomplish each fraction. Without access to a brachytherapy suite incorporated with anesthesia, the use of GA can potentially lead to significant increases in treatment duration and intra-fraction patient shifting, both of which can compromise treatment dosimetry and replicability, as the patient moves from the operating room to the simulator, and ultimately to the treatment room. Patients receiving BT for cervical cancer tend to require up to five fractions, with each session of GA requiring the access to significant resources. The safety of using intravenous sedatives for CS as alternatives to GA for HBT has been demonstrated by a variety of investigators in the last decade, but concerns remain over sedative-related side effects [12-14]. The increased resource burden resulting from the need for GA or CS to perform HBT, in various instances, can limit some patients from being able to undergo the interstitial component of HBT, putting this patient's population at significantly increased risk of local failure after EBRT and/or increased toxicity of organs at risk (OARs), as demonstrated in the Retro-EMBRACE study [3].

As expected, with recent changes and optimizations to the standard of care (EBRT + BT boost), widespread integration of new procedural techniques can be limited. Lack of access to brachytherapy-capable facilities and optimal treatments remain as major concern for patients with LACC, with a variety of barriers hindering access to care [15, 16]. If a patient presents to a brachytherapy center, which does not perform HBT, logistical factors, such as distance, may limit undergoing traditional intracavitary brachytherapy alone without interstitial needles, instead of seeking out other locations capable of performing HBT. Health disparity investigations have repeatedly shown limited access to radiation treatment for a wide variety of patients across the United States, and this trend is further exaggerated when examining access to brachytherapy [17-20]. As some clinics have been slow to transition from intracavitary brachytherapy to HBT due to insufficient resources and concerns of decreased treatment tolerance, finding alternative, efficient, and well-tolerated HBT techniques with decreased resource requirements has the potential to accelerate the increased adoption of HBT, and ultimately improve patients' outcomes.

The American Society of Anesthesiologists (ASA) defines "minimal sedation" as a drug-induced state with impaired cognitive function and physical coordination [21, 22]. However, patients respond normally to verbal commands, and airway reflexes and cardio-vascular functions are unaffected. The ability of patients to undergo procedures with minimal sedation allows for a variety of logistical improvements for both patients and clinics performing the procedure of interest. Given the potential benefits of more widespread adoption of HBT for patients with LACC, it would be important to determine the feasibility of performing HBT with minimal sedation in the outpatient setting. In the current study, the results of a single institution's minimalistic approach for outpatient HBT using only ASA-defined minimal sedation via oral medications were described.

Material and methods

The charts of patients with LACC, who underwent outpatient HBT treatments from June 2018 to May 2020 were retrospectively reviewed. After LACC diagnosis and initial consultations with gynecologic oncology and radiation oncology teams, all patients underwent treatment with concurrent chemotherapy and EBRT. Initial staging included an magnetic resonance imaging (MRI) that was used for treatment planning. All patients undergoing EBRT received a traditional whole pelvis intensity-modulated radiotherapy (IMRT) field, which treated the pelvis and at risk regional lymph nodes to 45 Gy, with simultaneous integrated boost to positive lymph nodes to 57.5 Gy, with extension to the peri-aortic nodes as warranted.

Following completion of EBRT treatment course and prior to HBT, all patients underwent examination under anesthesia (EUA), and Smit sleeve placement under general anesthesia or deep sedation. Pre-BT imaging consisted of cone-beam CT (CBCT), and a second MRI was not feasible. The decision to use interstitial needles was made either based upon the findings from EUA, the most recent CBCT, or if there was a perceived dosimetric advantage during the course of patient's brachytherapy, such as if a portion of the tumor was felt to be inadequately covered by a prior fraction of intracavitary brachytherapy.

Oral lorazepam and oxycodone/acetaminophen were prescribed prior to the first scheduled HBT date, and administered between 30-90 minutes before the procedure to achieve minimal sedation. Patients were then placed on the CT simulator table in supine position, with both knees flexed. Next, a vaginal vault was prepped with betadine, and a urinary catheter was placed into the bladder with the balloon inflated. Afterward, the HBT applicator (Utrecht interstitial CT/MR applicator set, Elekta) was placed with the tandem first inserted through the Smit sleeve, followed by the ovoids and vaginal spacer balloon (Alatus vaginal balloon, AngioDynamics). The needles were then advanced under CT guidance using sequential CT scans. After confirmation of satisfactory applicator and needle placement via sequential CT imaging, bladder fill was accomplished with diluted contrast along with filling of the vaginal spacer balloon. A final scan was taken to confirm applicator placement and for treatment planning, and patients were carefully transferred to a mobile treatment bed before being relocated to brachytherapy suite for connection to afterloader and treatment.

Both high-risk clinical target volume (HR-CTV) and organs at risk (OARs), including the urinary bladder, rectum, and sigmoid colon were delineated on the final treatment planning CT scan using Oncentra treatment planning software (Elekta). Dose prescription was guided

Table 1. Summary of patients' treatment details

Parameter	Results
Total patients treated	63
Total interstitial implants	244
Total needles placed	453
Median time for the entire procedure (from entry into CT sim to exit of HDR treatment room)	70 minutes (mean, 70.3 minutes; range, 54-100 minutes)
Median time after T&O insertion to complete interstitial needle insertion	9 minutes (mean, 9.8 minutes; range, 4-24 minutes)
Median needles placed in Utrecht applicator	2 needles (mean, 1.93 needles; range, 1-3 needles)
Median CT scans taken for needle advancement	3 scans (mean, 2.63 scans; range, 1-4 scans)

primarily based upon the initial EBRT dose and fractionation prescribed to the patient, with careful consideration of their pre- and post-EBRT extent of disease. HBT boost portion consisted of an additional 6 Gy per fraction for 5 fractions, as one of the recommended dose fractionations of the American Brachytherapy Society guidelines [23].

After treatment was completed, the applicator was removed on the treatment bed. If the patient experienced any bleeding, vaginal packing was placed and pressure held, until resolution of bleeding occurred. If bleeding persisted, the patient would be transferred to an exam table, and a pelvic exam would be performed to evaluate the cause of the bleeding for further management as needed, such as with vaginal sutures, Monsel solution, or silver nitrate.

Each treatment was delivered 2-5 days apart (on Tuesdays and Thursdays), with utilization of broad-spectrum antibiotics and additional analgesia prescribed at the discretion of the performing physician.

Results

A summary of patients and procedural details are depicted in Table 1, highlighting information regarding the total procedure duration, median time for interstitial needle insertion, and intra-procedural imaging. A total of 63 patients underwent HBT treatments under minimal sedation. Overall, 244 interstitial implants with 453 needles were placed via CT-guidance. All patients required only one total position shift (from the CT table to the mobile treatment bed).

The analgesic and anxiolytic doses are summarized in Table 2. In terms of analgesics, majority of patients used 10 mg oxycodone and 650 mg acetaminophen (77.9%), while roughly 15% of patients used lower doses, i.e., morphine or 15 mg oxycodone alone, and 6.6% of the implants were well-tolerated without any analgesics. With respect to anxiolytic usage, 8% of patients used between 0.5 and 1.0 mg prior to the procedure, whereas roughly 9% of patients used 2.0 mg, and about 5% of the implants were performed with no anxiolytic medication.

Bleeding occurred in 22.1% (54/244) (Table 3). All bleeding resolved with vaginal packing and pressure for 3 minutes (mean, 3.33 minutes; range, 1-8 minutes). No vaginal sutures or overnight admissions occurred due to vaginal bleedings, and no blood transfusions were administered.

In terms of procedure feasibility, sixty-one patients (96.8%, 61/63) tolerated the procedure without any additional intervention, while two patients (3.2%, 2/63)

Table 2. Details of medication used for minimal sedation

Parameter	% (*n*)
Analgesic medication	
10 mg oxycodone/650 acetaminophen	77.9 (190/244)
5 mg oxycodone/325 acetaminophen	7.4 (18/244)
5 mg morphine	3.7 (9/244)
4 mg morphine	1.2 (3/244)
2 mg morphine	1.2 (3/244)
15 mg oxycodone	2.1 (5/244)
No analgesic medication	6.6 (16/244)
Anxiolytic medication	
2.0 mg lorazepam	8.6 (21/244)
1.0 mg lorazepam	41.8 (102/244)
0.5 mg lorazepam	44.7 (109/244)
No anxiolytic medication	4.9 (12/244)
Medication combination	
Both analgesic and anxiolytic medication	91.39 (223/244)
Only analgesic, no anxiolytic medication	2.1 (5/244)
No analgesic, only anxiolytic medication	4.9 (12/244)
No analgesic, no anxiolytic medication	1.6 (4/244)

Table 3. Bleeding incidence

Parameter	Results
Post-treatment bleeding incidence	22.1% (54/244) of implants
Median bleeding resolution time (with vaginal packing and pressure)	3 minutes (mean, 3.33 minutes; range, 1-8 minutes)
Hospital admissions	0% (0/244) of implants
Blood transfusions	0% (0/244) of implants

required use of epidural anesthesia to complete their treatments. None of the patients in the series required a transition to general anesthesia for the procedure.

Discussion

The performance of HBT and choice of anesthesia varies greatly per institutional preference, with many centers preferring to treat patients with the historical standard of general anesthesia, spinal/epidural anesthesia, or conscious sedation [11, 12]. Image guidance for treatment planning can vary depending on resources, with some centers utilizing CT- or MRI-based treatment planning techniques [3, 4]. As these factors lead to a significant increase in required resources, and the adoption of HBT has remained limited despite significant data suggesting substantial benefits for patients with LACC [1, 3, 15, 16].

Furthermore, there are major disparities in patients' access to radiation treatment, often adding enormous hardship to cancer patients in need of radiation therapy as part of their treatment plan [15-20]. Some patients are required to travel to distant locations, often contributing to significant socio-economic, emotional, and physical burdens. Further exacerbating the issue, only a portion of EBRT-performing radiation treatment centers perform gynecologic brachytherapy, and even fewer perform HBT despite significantly improved outcomes compared with intracavitary brachytherapy alone.

Our technique for image-guided adaptive HBT represents a highly efficient, reproducible, and well-tolerated method for treatment delivery, which requires substantially fewer resources than those frequently utilized by many BT-performing centers. The lack of need for a formal anesthesia team for each brachytherapy treatment permits the ability to perform HBT in a free-standing setting removed from a hospital or operative room, or in a setting with limited resources. The low overall treatment time (median, 70 minutes) represents a significant possible logistical benefit for improved clinic workflow and ease of adoption of the technique. The bleeding complication rate of 22.1%, which did resolve after about three minutes of vaginal packing and pressure, must be considered if adopting this technique.

Potential advantages of this procedure include an increase in HBT utilization, along with decreases in costs and staffing needs. This approach does not prevent nor complicate transition to epidural anesthesia if necessary, allows for faster procedural and anesthesia recovery times, shorter overall treatment durations, and less resources.

There are a few limitations worth acknowledging in the study. First, objective pain scores were not obtained. Comparison of objective pain scores of this technique with minimal sedation versus pain scores with general anesthesia could be beneficial. Second, a pre-brachytherapy MRI and/or MRI-based brachytherapy planning could improve tumor coverage and decrease dose to OARs. Third, in this series, this technique did require at least one GA or sedation procedure for Smit sleeve placement, and the cost and resources needed must be taken into account. In low-resource areas, without any operative capability, this method might not be reproducible. Fourth, to perform HBT under minimal sedation requires an efficient, organized team, and unwavering emphasis on patient communication. This technique might not be generalizable to other treatment centers depending on available resources. Fifth, careful patients' selection is necessary. While patients with a wide variety of comorbidities, such as anxiety, claustrophobia, chronic pain conditions, and post-traumatic stress disorder were included in this investigation, these variables were not accounted for when analyzing treatment options and medication doses. There are selected patients, who will have difficulty in cooperating with the high-acuity aspects of the treatment, such as making an effort to limit their movements. Ultimately, the decision to transition to epidural anesthesia in the two patients was made from a combination of factors, taking into account the patient's comfort level and concerns over treatment feasibility. Sixth, there are concerns about post-traumatic stress disorder and long-term impacts on sexual intercourse in patients undergoing BT [24]. Whether the utilization of general anesthesia helps to reduce the emotional trauma of patients undergoing BT remains a topic for further investigation, and a patient-centered, individualized approach must be taken to weigh the negatives of performing the procedure with minimal sedation versus the associated risks of multiple successive rounds of general anesthesia. Last, this series used minimal sedation for the placement of a maximum of 3 needles. It is unknown through this work if 4 or more needles would still be feasible in this technique.

Ultimately, we optimistically describe this method with the goal of encouraging more physicians and BT-performing centers to utilize HBT. As gynecologic malignancies remain a significant contributor to female mortality across the world, especially for underserved populations, this protocol has the potential to significantly impact oncologic outcomes in patients with LACC, especially in areas with limited access to operating rooms, brachytherapy suites, and MRIs. Our study provides a foundation for numerous further investigations, including thorough evaluations of patient-reported pain levels, quality of life, treatment completion rates, and patient's treatment satisfaction. Furthermore, trials of low-dose gabapentin, duloxetine, or other opioid synergistic therapies warrant consideration to further improve procedure tolerance and pain levels. Finally, a much larger series of HBT using minimal sedation would be needed to ensure the non-inferiority of this technique vs. HBT with general anesthesia.

Conclusions

In our series, the treatment of HBT for cervical cancer with minimal sedation was achievable at a high percentage (96.8%). The ability to perform HBT without GA or conscious sedation for each fraction has the potential to increase efficiency, cost-effectiveness, treatment tolerance, and patient compliance, while providing a reasonable option for IGABT in areas with limited resources. Given the significant mortality of LACC worldwide, increasing access to HBT is of critical importance. By decreasing

the required staff and associated resources to perform each procedure, this minimalistic approach may enable more widespread adoption of HBT, which would be expected to lead to improved oncologic outcomes in patients with LACC. Further investigations using this technique are warranted to assess for effects on patient-reported quality of life, patient's treatment satisfaction, treatment duration, and completion rates.

Ethics statement

This study was IRB-approved (IRB No.: 2107027282) by the University of Arizona College of Medicine – Phoenix. The study was exempt from consent due to the retrospective review nature of the study.

Disclosure

The authors report no conflict of interest.

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