

Novel anesthetic technique for combined intracavitary and interstitial brachytherapy for cervix cancer in an outpatient setting

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Abstract

Purpose: To determine the feasibility and safety of outpatient combined intracavitary and interstitial brachytherapy for cervix cancer with sedation and local anesthesia.

Material and methods: We included patients diagnosed with non-metastatic cervix cancer and have completed brachytherapy between December 2015 and December 2016. Moderate to deep sedation was achieved using intravenous midazolam, propofol, fentanyl, and oxycodone. Local anesthesia was achieved with 2% lignocaine gel and a paracervical block containing a mixture of 1% ropivacaine, 2% lignocaine, and 1 : 1,000 adrenaline. Ceftriaxone and ondansetron were given prophylactically. Physiologic monitoring was performed throughout and pain scores were recorded using the Numeric Rating Scale. Follow-up was conducted at 8 weeks from the last fraction of brachytherapy. The feasibility and safety endpoints were a post-anesthesia discharge score (PADS) of 9 or above, and no grade 3 or above adverse events, respectively.

Results: A total of thirty-five brachytherapy insertions were carried out on nine patients. The median age of the patients was 56 years (range, 40-65). Eight patients had American Society of Anesthesiologists' physical status of I or II, and one had a status of III. The mean duration of the insertion was 39 minutes (standard deviation [SD] = 14), during which no adverse events occurred. There was no significant nausea or vomiting post-sedation. The median pain scores post-insertion and during recovery were 0 (range, 0-6) and 0 (range, 0-7), respectively. At discharge, all patients had pain scores of 0 and maximum PADS of 10. The mean time to discharge was 4.1 hours (SD = 0.95). There were no brachytherapy-related admissions or complications.

Conclusions: Outpatient combined intracavitary and interstitial brachytherapy for cervix cancer with sedation and local anesthesia is feasible and safe. This could potentially lead to significant cost savings.

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Key words: anesthetic technique, cervix cancer, interstitial brachytherapy.

Purpose

Brachytherapy plays a pivotal role in the curative treatment of locally advanced cervix cancers, allowing high doses to be delivered to the cervix while relatively sparing other pelvic organs [1]. Cervix brachytherapy involves insertion of an intracavitary applicator, which has intrauterine and intravaginal components. When dosimetric coverage of the cervix tumor cannot be sufficiently provided by the intracavitary applicator alone, for example in tumors with parametrial or pelvic sidewall extension, addition of interstitial needles has demonstrated excellent outcomes and has been shown to improve coverage, local control, and survival [2,3,4]. The impor-

tance of improved tumor coverage with interstitial needles has been underlined by guidelines from both the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology, and the American Brachytherapy Society [5,6], and its use coupled with image guidance is expected to increase. Without adequate anesthesia, applicator and needle insertion during cervix brachytherapy will invariably cause pain and distress. Moreover, the insertion of interstitial needles into the parametrium can cause more severe pain than that caused by the intracavitary applicator alone [7]. Effective anesthesia is therefore needed to allow brachytherapy to be carried out.

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The optimal anesthetic technique for cervix brachytherapy has not been recognized by published data. In practice, general anesthesia and spinal anesthesia are preferred [8]. This, however, may be burdensome for resource-limited institutions. Outpatient sedation may provide a viable alternative, but there has been no studies addressing its adequacy for combined intracavitary and interstitial brachytherapy in cervix cancer. The purpose of our study is to report our initial experience regarding the feasibility and safety of performing combined intracavitary and interstitial high-dose-rate (HDR) brachytherapy for cervix cancer with a novel approach of intravenous sedation and local anesthesia in an outpatient setting.

Material and methods

We obtained approval of the study from our Institutional Review Board. We analyzed and collected data retrospectively from the hospital electronic records. Patient data were managed in strict accordance with our institutional information governance rules.

We evaluated all patients diagnosed with non-metastatic, histologically confirmed cervix cancer, and treated with combined intracavitary and interstitial HDR brachytherapy at the National University Cancer Institute in Singapore between December 2015 and December 2016. All patients received pelvic external beam radiotherapy (EBRT) with a standard four-field arrangement to a total dose of 50.4 Gy in 28 fractions with concurrent weekly cisplatin chemotherapy at a dose of 40 mg/m². Three patients had pelvic nodal involvement and received a nodal boost of 5.4 Gy in 3 fractions using parallel-opposed beams with midline shields. Fourth patient had both para-aortic and pelvic nodal involvement and received a nodal boost of 5.4 Gy in 3 fractions via intensity-modulated radiotherapy technique. We commenced brachytherapy within two days of completion of EBRT, with no more than two fractions delivered per week and consecutive fractions given at least a day apart to allow sufficient normal tissue recovery. Eight patients received four fractions of HDR brachytherapy using a combined intracavitary and interstitial approach, while one patient received only three fractions after sustaining an unrelated fall. We prescribed 7 Gy for each fraction of brachytherapy to the high-risk clinical target volume. We used interstitial blunt-ended needles in conjunction with the Utrecht (tandem and ovoid) intracavitary applicator. Our indications for interstitial needle use were as follows: 1) Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IIB or above, or 2) FIGO stage IB2 or IIA2, and in which the vagina was assessed to be narrow clinically.

All patients had a pre-anesthetic assessment and were assigned an American Society of Anesthesiologists' (ASA) physical status classification. On the day of the brachytherapy, patients were fasting for six hours prior to anesthesia. No premedications were given. Patients were draped and prepared in the lithotomy position in a dedicated brachytherapy suite equipped with full resuscitation facilities. All received supplementary oxygen at 2 liters per minute via nasal cannulas. The radiation oncology team comprising of the radiation oncologist,

assisting registrar, registered nurse, radiation therapist, and medical physicist was assembled before the procedure commenced. An anesthesiologist was present throughout the procedure.

Our anesthetic regimen consisted of a combination of intravenous midazolam, propofol, fentanyl, oxycodone, and local anesthesia. The anesthesiologist administered all intravenous drugs. An initial dose of midazolam was given at the start of the insertion, and further dosing given as required to achieve adequate sedation throughout the insertion. Propofol was given as a slow infusion via a syringe pump. Next, fentanyl and oxycodone were administered. Finally, local anesthesia was provided by 10 ml of 2% lignocaine gel applied to the vaginal canal and a paracervical block consisting a mixture of 5 ml of 1% ropivocaine, 5 ml of 2% lignocaine, and 0.1 ml of 1 : 1,000 adrenaline, administered at one, four, seven, and ten o'clock positions around the cervix. Ceftriaxone and ondansetron were administered intravenously for prophylaxis against infection and nausea, respectively. A Foley catheter was inserted after sedation was achieved, following which insertion of the intracavitary applicator and interstitial needles by the radiation oncologist began. The time at which vaginal packing with gauze was completed marked the end of the insertion.

We used a Modified Ramsay Sedation Scale to grade the level of sedation (Appendix 1) [9]. The nurse performed physiologic monitoring on the patient's blood pressure (non-invasive method), heart rate, respiratory rate, and pulse oximeter reading every 5 minutes during the insertion and every 15 minutes after the patient has recovered from sedation. Propofol infusion was stopped once vaginal packing was completed to allow recovery from sedation. The time at which the patient became fully awake (Modified Ramsay Sedation Score of 1 or 2) marked the time of recovery from sedation.

Upon completion of the insertion, the patient was returned to the supine position with knees straightened comfortably and transported to the computed tomography (CT) simulator adjacent to the brachytherapy suite for evaluation of the applicator and needle positions. During CT simulation, uterine perforation and pelvic blood from vessel perforation could be detected. Subsequently, patients were placed in the recovery area adjacent to the suite under the care of the nurse while waiting for dosimetric planning to be done. Patients reported any post-insertion pain, which was recorded by the nurse using the 11-point Numeric Rating Scale from the time of recovery to discharge [10]. Patients could receive 1 g of intravenous paracetamol on a pro re nata (prn) basis during recovery. We graded and recorded adverse effects using the Common Terminology Criteria for Adverse Events version 4.03 [11].

When dosimetric planning was completed, we delivered brachytherapy using a remote afterloader device (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) with ¹⁹²Ir seeds. We recorded the total dwell time of the ¹⁹²Ir seeds, which constituted the brachytherapy treatment time. Once the intended dose was delivered, we removed the applicator and interstitial needles, as well

as the Foley catheter, in the suite. Before being discharged, the patients had a visual inspection of the cervix to ensure hemostasis was achieved. We used the post-anesthesia discharge score (PADS) to determine if the patients were fit for discharge (Appendix 2) [12]. Patients returned for their first post-treatment follow-up at eight weeks from the time of completion of the last fraction of brachytherapy.

For statistical analysis, the mean, median, and standard deviation values were calculated using Microsoft Excel 2010 (version 14.0) software.

Results

A total of thirty-five combined intracavitary and interstitial brachytherapy insertions were carried out on nine patients. The patients' characteristics are shown in Table 1.

Table 2 shows the intravenous drug doses used in our anesthetic protocol. The mean doses for midazolam, propofol, fentanyl, and oxycodone were 0.03 mg/kg⁻¹ (SD 0.01), 1.68 mg/kg⁻¹ (SD 1.14), 1.13 µg/kg⁻¹ (SD 0.45), and 0.08 mg/kg⁻¹ (SD 0.01), respectively per insertion. We administered local anesthesia for all patients in proportions stated in the previous section. Each patient received 1 g of ceftriaxone per insertion. The mean dose of ondansetron used per insertion was 0.08 mg/kg⁻¹ (SD 0.02). No patients required reversal agents from intravenous sedatives. We did not observe any episodes of hemodynamic or cardiovascular instability. One patient, during

her third fraction of brachytherapy, experienced transient desaturation due to apnea to below 90% on pulse oximeter reading. A senior anesthesiologist was present and oxygen saturation was restored to above 95% within ten seconds by insertion of a nasal airway and manual bag and mask ventilation. This patient did not require intubation or reversal agents as spontaneous ventilation returned promptly with no significant changes hemodynamically. No desaturation occurred in all other insertions.

The median number of interstitial needles inserted was 2 (range, 1-4). The mean values for duration of insertion, recovery time from sedation and dwell time of the ¹⁹²Ir seeds are shown in Table 3. The median Modified Ramsay Sedation Score was 4 (range, 3-6), corresponding to a satisfactory level of sedation. Patients did not report any nausea or had vomiting after they had recovered from sedation. No uterine perforations or suggestion of uterine vessel perforations were observed.

We observed good analgesic effect for all insertions. The median pain score immediately post-insertion and at the recovery area were 0 (range, 0-6) and 0 (range, 0-7), respectively. There were only three insertions in three separate patients, during which pain scores of greater than 0 were reported, two of which occurred immediately post-insertion. These three patients each received a prn dose of 1 g of intravenous paracetamol. Hemostasis was achieved following removal of the applicator and needles in all patients. The mean time from the start of the procedure to the patient's discharge was 4.1 hours (SD 0.95). At the time of discharge, all patients had pain scores of zero as well as maximum PADS of 10, and were deemed fit for discharge. There were no brachytherapy-related hospital admissions in the peri-procedural period and up to eight weeks from the date of the last fraction of brachytherapy. There were no instances of post-insertion pelvic infections.

Table 1. Characteristics of patients receiving brachytherapy

Characteristics	Number
Age, years; median (range)	56 (40-65)
Weight, kg; mean (range)	62.0 (46.0-100.0)
Ethnicity	
Chinese	7
Malay	1
Arab	1
Reproductive history	
Nulligravida patients	2
Pregnancies; median (range)	2 (1-6)
Deliveries; median (range)	2 (1-6)
ASA PS classification	
I	3
II	5
III	1
FIGO stage	
IB2	1
IIA2	1
IIB	4
IIIB	3

ASA PS – American Society of Anesthesiologists' physical status, FIGO – Fédération Internationale de Gynécologie et d'Obstétrique

Table 2. Intravenous drug doses for anesthetic regimen used in brachytherapy

Drug	Mean	SD
Midazolam (mg/kg ⁻¹)	0.03	0.01
Propofol (mg/kg ⁻¹)	1.68	1.14
Fentanyl (µg/kg ⁻¹)	1.13	0.45
Oxycodone (mg/kg ⁻¹)	0.08	0.01
Ondansetron (mg/kg ⁻¹)	0.08	0.02
Ceftriaxone (g)	1	-

Table 3. Time spent on insertion, recovery, treatment, and to discharge

Variable	Mean per insertion	SD
Duration of insertion (mins)	39	14
Duration of recovery from insertion (mins)	58	20
Dwell time of ¹⁹² Ir (mins)	9	3
Time from insertion to discharge (hours)	4.1	0.95

Discussion

Cervix cancer brachytherapy is a painful procedure that can cause significant discomfort. Patients who undergo the procedure, potentially experience pain from one or more causes. Uterine stimulation from the central tandem activates sympathetic autonomic afferents at the T10 to L1 spinal levels, resulting in lower abdominal pain. Distension of the cervix by the ovoid or ring applicator stimulates parasympathetic autonomic afferents at the S2 to S4 levels, resulting in lower back pain. Vaginal packing with gauze, a necessary step in brachytherapy to displace the bladder and rectum from the high dose region, can cause similar lower back pain [13]. Piercing of the paracervical tissue by the interstitial needles results in transmission of pain sensation via sensory and sympathetic pathways to the lateral spinothalamic tracts [14]. Ineffective management of these sources of pain may lead to poor tolerance of the procedure, resulting in suboptimal placement of the applicator, needles, or vaginal packing, and can result in poorer treatment outcomes [15].

Midazolam and propofol are both widely used sedative drugs for day procedures, and each of them is often coupled with fentanyl and oxycodone to provide analgesia. Midazolam has an onset of action in one to two minutes, and has been associated with frequent hypoxemia and apnea [16]. Propofol is a highly lipophilic hypnotic drug that crosses the blood-brain barrier quickly. In addition to its excellent amnesic effect, propofol has a rapid onset of action as well as a rapid recovery profile that is superior to midazolam. However, the respiratory depressant effects of propofol, as well as potential drop in cardiac output, have been well documented [17]. Synergistic effects could be achieved by using propofol together with midazolam, allowing doses of each drug to be reduced so as to decrease the potential side effects from each, but yet achieve the desired level of sedation [18].

Evidence on the optimal anesthetic regimen for combined intracavitary and interstitial cervix brachytherapy is lacking. In practice, general and spinal anesthesia are frequently used for gynecological brachytherapy, perhaps because they are perceived as allowing for a more controlled environment for proceduralist to perform the insertion [6]. However, not only does it necessitate airway management. Lim *et al.* has shown a higher rate of complications when general anesthesia was used compared to moderate sedation in intracavitary brachytherapy [19]. Local vaginal anesthesia, moderate sedation, and spinal anesthesia have all been previously described for intracavitary applicator insertions [7,8,19,20]. However, their role when combined with interstitial needle insertion, a perceivably more painful procedure, has not been evaluated. Paracervical blocks have been shown to be an effective local anesthetic technique for gynecology procedures [14,21]. An approach using a combination of sedation and local anesthesia for cervix brachytherapy may provide a viable alternative to general anesthesia.

Our study demonstrated that during the procedure, adequate sedation and good pain relief were achieved, and patients' safety was not compromised. There were no adverse events encountered during the procedure. In addition,

we did not experience any peri-procedural morbidity or complications. The rate of intra-procedure hypoxemia in our study was 2.9% and is in line with published data on propofol used for sedation purposes, and if managed appropriately, has not been shown to result in adverse outcomes [22,23]. We did not measure the serum levels of ropivacaine and lignocaine in our patients, but limiting the dose to that used in the paracervical block mixture appears safe and comparable to published results on safety [24]. Postoperative nausea and vomiting that have been reported with the use of intravenous fentanyl were not seen in our study, likely due to the low doses used and the known antiemetic efficacy of ondansetron in the postoperative setting [25,26]. Oxycodone was added to increase the analgesic efficacy of the regimen without having to increase the dose of fentanyl, thereby keeping the emetogenicity from fentanyl low. Intravenous antibiotics are commonly given intraoperatively to reduce the risk of post-surgical infection [27]. We did not observe any post-procedure infection with the use of prophylactic ceftriaxone.

There were no major logistical barriers in implementing this regimen. It does require meticulous cooperation between various team members and the hospital for its successful implementation. Our study has a few important implications. Many centers in the world now face increasing pressures in providing quality healthcare with limited resources in the face of rising patient numbers. Continued efforts are made to find healthcare solutions that are centered on quality, efficiency as well as affordability. To date, there have been no cost-effectiveness studies on different anesthetic techniques for brachytherapy. The well-accepted practice of performing brachytherapy under general anesthesia has been associated with a higher rate of complications [19]. This may translate to increased costs for both the patient and the hospital, because of unplanned interventions or admissions when complications occur. Other potential drivers of costs associated with general anesthesia include anesthetic charges, the need for operating theatre time, and a longer duration of patient recovery from anesthesia and hence, a longer time to discharge. Performing brachytherapy in the outpatient setting with sedation and local anesthesia can potentially lead to significant cost savings for both the patient and the hospital, and a prospective study should be undertaken to quantify the benefits. This in turn could have major implications on hospital and healthcare policies in a cost-conscious environment. In addition, from the patient's perspective, an anesthetic technique that is efficacious, safe, convenient and lower in cost is certainly preferable. We hope that this feasibility and safety study can provide a platform for further studies to shed light on the cost-effectiveness of this approach.

There are a few limitations to our study. Firstly, the sample size for the number of insertions, as well as the number of patients involved, were small. Secondly, the qualitative aspect of the patients' experience, such as fear and anxiety, were not evaluated. These psychological aspects may form an important part of the patients' overall experience and affect compliance, and contribute to psychological stress [28]. Thirdly, the radiation oncologist's satisfaction in the

anesthetic regimen was not assessed, as this may potentially have an impact on ease placement of the applicator and needles. Further studies are needed to understand the qualitative experience of both the patient and the proceduralist, and their potential impact on treatment outcomes.

Conclusions

Our study demonstrated that combined intracavitary and interstitial brachytherapy can be carried out under sedation and local anesthesia in an outpatient setting with adequate level of sedation and good analgesia, being achieved without any compromise on patients' safety. This could potentially lead to significant cost savings for both the patient and the hospital.

Disclosure

Authors report no conflict of interest.

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Appendix 1. Modified Ramsay Sedation Scale used to grade the level of sedation [8]

Level	Response
1	Patient is anxious, agitated, or restless
2	Patient is cooperative, oriented, and tranquil
3	Patient is asleep, brisk response to loud auditory stimulus
4	Patient is asleep, sluggish response to loud auditory stimulus
5	Patient has no response to loud auditory stimulus, but does respond to painful stimulus
6	Patient does not respond to painful stimulus

Appendix 2. Post-anesthesia discharge scoring system used to determine fitness for discharge [11]

1. Vital signs
2 = Within 20% of preoperative value
1 = 20-40% of preoperative value
0 = > 40% preoperative value
2. Activity and mental status
2 = Oriented x3 and has a steady gait
1 = Oriented x3 or has a steady gait
0 = Neither
3. Pain, nausea, and/or vomiting
2 = Minimal
1 = Moderate, having required treatment
0 = Severe, requiring treatment
4. Surgical bleeding
2 = Minimal
1 = Moderate
0 = Severe
5. Intake and output
2 = Has had PO fluids and voided
1 = Has had PO fluids or voided
0 = Neither

Total score is 10; score ≥ 9 considered fit for discharge