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Original Article

Time-action and patient experience analyses of locally advanced cervical cancer brachytherapy

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ABSTRACT

BACKGROUND AND PURPOSE: Although MRI-based image guided adaptive brachytherapy (IGABT) for locally advanced cervical cancer (LACC) has resulted in favorable outcomes, it can be logistically complex and time consuming compared to 2D image-based brachytherapy, and both physically and emotionally intensive for patients. This prospective study aims to perform time-action and patient experience analyses during IGABT to guide further improvements.

MATERIALS AND METHODS: LACC patients treated with IGABT were included for the time-action (56 patients) and patient experience (29 patients) analyses. Times per treatment step were reported on a standardized form. For the patient experience analysis, a baseline health status was established with the EQ-5D-5L questionnaire and the perceived pain, anxiety and duration for each treatment step were assessed with the NRS-11.

RESULTS: The median total procedure time from arrival until discharge was 530 (IQR: 480–565) minutes. Treatment planning (delineation, reconstruction, optimization) required the most time and took 175 (IQR: 145–195) minutes. Highest perceived pain was reported during applicator removal and treatment planning, anxiety during applicator removal, and duration during image acquisition and treatment planning. Perceived pain, anxiety and duration were correlated. Higher pre-treatment pain and anxiety scores were associated with higher perceived pain, anxiety and duration.

CONCLUSION: This study highlights the complexity, duration and impact on patient experience of the current IGABT workflow. Patient reported pre-treatment pain and anxiety can help identify patients that may benefit from additional support. Research and implementation of measures aiming at shortening the overall procedure duration, which may include logistical, staffing and technological aspects, should be prioritized.

Keywords: Uterine cervical neoplasms; Brachytherapy; Pain; Anxiety; Duration of therapy; Workflow

Introduction

Cervical cancer is the fourth most common type of cancer in women worldwide, with an estimated 604,000 newly diagnosed patients and 342,000 deaths in 2020 (1). The treatment of choice for locally advanced cervical cancer (LACC) is definitive radiochemotherapy, consisting of concomitant external beam radiation therapy (EBRT) and chemotherapy, followed by image guided adaptive brachytherapy (IGABT) (2,3). During interstitial + intracavitary (IS + IC) IGABT, a radioactive source is guided through an applicator implanted in the vaginal cavity and uterus, and through interstitial catheters placed

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inside or near the tumor tissue (4). With MRI, precise volumetric delineation of the individual patient's tumor target (residual gross tumor volume (GTVRES), high risk clinical target volume (CTVHR) and intermediate risk clinical target volume (CTVIR)) in relation to surrounding organs at risk (OARs) allows for personalized brachytherapy dose optimization compared to historical use of one-size fits all standard treatment plans. Favorable outcomes regarding local control, survival and toxicity have been reported with the introduction of MRI-based IGABT (5,6). Although clinical outcomes have improved, the current MRI-based IGABT procedure can be logistically complex and time-consuming compared to 2D image-based brachytherapy, and both physically and emotionally intensive for patients. Several studies looked into the patient's experience before, during and after radiochemotherapy for LACC and reported impairments in health-related quality of life (HR-QoL) and patient reported symptoms. Early symptoms such as diarrhea, urinary frequency and fatigue, start early on and peak at the end of EBRT when IGABT starts. While most of these symptoms resolve during the first three months after treatment, some symptoms persist or even increase after treatment and have a long-term impact on HR-QoL (7–9). Several studies found that patients reported pain and distress during IGABT were overall mild and patients experienced little physical and emotional discomfort. However, certain patients experienced more severe pain and anxiety (10–13). Other studies looked at the workflow of IGABT and included a variety in scheduling regimes and holistic care (14–16). Still little is known about the durations and patients' experiences of separate IGABT treatment steps. The objective of this prospective study is to perform time-action and patient experience analyses for each IGABT treatment step in order to give an overview of the current workflow and the patient experience. This knowledge is of importance to help identify and prioritize procedural aspects of which further improvement may positively impact patient wellbeing.

Materials and methods

Patient population

The recruitment of participants took place at the Erasmus MC, Rotterdam, the Netherlands, from April 2021 to February 2022. During this period, patients treated for LACC with IGABT with either the Utrecht or Venezia applicator (Elekta AB, Stockholm, Sweden) were first included for the time-action analysis. After implementation of the time-action analysis, eligible patients were approached and asked for consent for an additional patient experience analysis. The exclusion criterion for the patient experience analysis was inability to understand the study questionnaire and protocol because of a language barrier. Patients in our institute can be treated with a single fraction procedures (1 fraction per implantation), and a double fraction procedure (2 fractions per implantation with at least 6 hours in between fractions) depending on logistics (e.g., scheduled OR time) and to ensure that the maximum overall treatment period and treatment objectives are within EMBRACE II protocol. Only single fraction procedures were included in the time-action and patient experience analyses because they were more frequently performed in our department in comparison to double fraction procedures. All participants included in the patient experience analysis gave informed consent before any study-related procedures were performed. The study was approved by the Institutional Review Board of Erasmus MC, Rotterdam, the Netherlands (protocol code MEC-2021-0336, date of approval 13-04-2021).

Brachytherapy procedure

Treatment procedures were conducted according to the EMBRACE II protocol (6). This included 45 Gy EBRT in 25 fractions (with, if indicated, a simultaneous integrated nodal boost), followed by 3 or 4 high-dose-rate IGABT fractions, aiming for a total cumulative (EBRT + IGABT) CTV_{HR} D_{90} of 90–95 Gy $EQD2_{10}$. A dedicated IGABT team on rotating basis was assigned to the IGABT treatment, including radiation oncologists, medical physicist, radiotherapy technologists, nurses, anesthesiologist, OR assistant and personnel in training. The average number of fractions per day was 3 (range: 1–5). The standard sedation protocol during LACC IGABT consisted of spinal anesthesia during applicator implantation. In case of contraindications, fear, or failure of spinal anesthesia, general anesthesia was used. Additional on demand anxiolytic medication (benzodiazepine) and analgesia (paracetamol, NSAID, morphine or morphine derivatives) were given after implantation according to the anesthetist's prescription. Family members are allowed to visit the short stay unit for support during the treatment. The IGABT procedure consisted of several treatment steps:

1. Preparation of implantation: the patient enters the department's short stay unit, is checked by the nurse (heart rate, blood pressure, temperature, oxygen saturation, awareness) and is prepared for transfer to the operating room.
2. Applicator implantation: the patient receives spinal or general anesthesia and a sterile field is created. Thereafter, a urinary catheter and a brachytherapy applicator with interstitial catheters are inserted, after which vaginal packing is applied, and the applicator is fixed. Following gadolinium markers are placed inside the tandem and ovoids, and the patient is transferred to the recovery room.
3. Recovery from implantation: in the recovery room, vital signs of the patient are monitored while the patient recovers from the implantation.

4. Waiting before imaging: optionally, the patient is transferred to the short stay unit after recovery to wait until the MRI scanner is available.
5. Image acquisition: the patient is brought to the imaging room where the bladder is filled according to standard protocol and MR, or by exception CT, images are obtained.
6. Treatment planning: the patient is allocated to the short stay unit until the treatment plan is finalized. Pain is regularly monitored by a nurse.
   a. The radiation oncologist delineates the OARs (bladder, rectum, sigmoid and bowel) and target volumes (GTV_{RES}, CTV_{HR}, CTV_{IR}) in MIM (MIM Software Inc., Cleveland, OH, United States). These structures are verified by another radiation oncologist.
   b. In parallel, the radiotherapy technologist reconstructs the applicator, catheters, and ICRU points in Oncentra Brachy version 4.6 (Elekta AB, Stockholm, Sweden), and verifies the results with another radiotherapy technologist.
   c. When the delineation and reconstruction are approved, an initial treatment plan is made by the radiotherapy technologist and verified or further optimized by the radiotherapy technologist, radiation oncologist, and medical physicist. When the treatment plan is approved, the treatment plan is uploaded to the afterloader and the patient is transferred to the treatment room.
7. Treatment delivery: the transfer tubes of the afterloader are connected to the applicator and catheters, and the bladder is filled according to protocol. After a dummy source has checked all channels, the patient is irradiated.
8. Applicator removal: the radiation oncologist removes the applicator and catheters.
9. Recovery: the patient is transferred to the short stay unit to recover until the patient is fit to be discharged.

Data collection

A time-action analysis was done to determine the efficiency and identify and prioritize improvements for the IGABT workflow. A time-action analysis is a tool to objectively determine the level of efficiency of a procedure by measuring the duration and frequency of different actions. It can be used to for several purposes such as: (1) Providing detailed insights of the limitations and errors of a procedure which can be used for clinically driven technological developments, (2) Evaluate and compare new instruments and techniques with standard procedures, and (3) Measure operator performance and determine learning curves (17–20). The time-action analysis included a standardized form, including steps and sub-steps which altogether define the complete IGABT procedure, on which the radiation oncologists, radiotherapy technologists and nurses reported the start and end times per treatment step, described in the previous section. If needed, additional comments to elucidate on delays, deviations or special circumstances were added. To verify accuracy, the start and end times were randomly assessed by the research team during the treatment day and cross-referenced with the electronic medical record (EMR).

To establish a baseline health status for the patient experience analysis during treatment, the EQ-5D-5L questionnaire was handed out in step 1 of the treatment (21). The EQ-5D-5L questionnaire is a validated measure for health status and consists of a self-reported health status and an EQ-VAS score (22,23). The self-reported health status consists of the following aspects: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each aspect has five optional response levels of severity: no problems, slight problems, moderate problems, severe problems, and extreme problems. From the response level of each of the five aspects, a health index (0 = dead, 1 = full health) was calculated according to the model of Versteegh et al. (24). The EQ-VAS provides a quantitative measure of the patient's perception of their overall health on a visual analogue scale (0 = worst imaginable health, 100 = best imaginable health) (21). During all other treatment steps, perceptions of pain, anxiety and duration (i.e., how long the patient felt the step lasted) were assessed, each with an 11-point numeric rating scale (NRS-11) (0 = perfect situation, 10 = worst imaginable situation). The NRS-11 is a reliable, validated and recommended questionnaire to assess pain of in cancer patients and has also been adapted to measure anxiety (25–30). For consistency, the NRS-11 was also used to measure the perceived duration. A score of 1–4 was categorized as mild, 5–6 was categorized as moderate, and 7–10 was categorized as severe (31). The NRS-11 was handed out at the beginning of the day. Patients registered the perceived pain, anxiety and duration after each procedure step.

Statistical analysis

To examine whether there were significant differences between the time, perceived pain, anxiety and duration per treatment step, a Friedman test was conducted and a post-hoc analysis with Wilcoxon signed-rank test was performed with Bonferroni corrections applied on the significance level α ($\alpha_{time} < 0.0063$, $\alpha_{pain,anxiety,duration} < 0.0056$). Furthermore, a Wilcoxon signed-rank test was done to determine the impact of baseline health status (EQ-5D-5L) and the type of anesthesia on the perceived pain, anxiety and duration scores, and a Kruskal-Wallis H test was conducted to test the influence of the number of fractions per day on the total treatment time and patient experience. In addition, Spearman's rank-order correlations were determined among the perceived pain, anxiety, duration, time and the number of needles used. The statistical analysis was performed using MATLAB and the Statistical and Machine Learning Toolbox Release 2020a (The MathWorks, Inc., Natick, MA, United States).

Table 1
Procedure characteristics

	Time-action analysis	Patient experience analysis
Total number of single fraction procedures	135	70
Anesthetics		
Spinal anesthesia	106	61
General anesthesia	29	9
Applicator		
Utrecht applicator	30	20
Venezia applicator	105	50
Imaging modality		
MRI	127	68
CT	8	2
Number of needles used: median (range)	6 (1–10)	5 (2–8)

CT = computed tomography; MRI = magnetic resonance imaging.

Results

Time-action analysis

In total 56 patients (135 single fraction procedures) were included in the time-action analysis. The procedure characteristics are reported in Table 1. The median procedure time with interquartile range (IQR) from arrival at the department until discharge was 530 (IQR: 480–565) minutes with a median treatment time from anesthesia to applicator removal of 354 (IQR: 319–377) minutes. The time per treatment step is depicted in Fig. 1. Treatment planning (delineation, reconstruction and optimization) was the most time-consuming step and took 175 (IQR: 145–195) minutes. Self-reported comments were clustered by topic and analyzed for optimization purposes. The comments were regarding the workflow (75), difficulty in tasks (32), training and education of new staff (25), concurrent tasks (25), technical difficulties (18), and time notation uncertainties (12).

Patient experience analysis

In total 29 patients (70 single fraction procedures) were included in the patient experience analysis. Nine patients were excluded due to inability to understand the study questionnaire and protocol because of a language barrier, and 9 patients because they did not give informed consent. The patients included had a mean age of 47 (range: 30–77) years. According to the International Federation of Gynaecology and Obstetrics (FIGO) 2018 the stage distribution was, 4 (14%) IB, 5 (17%) IIB, 1 (3%) IIIA, 1 (3%) IIIB, 15 (52%) stage IIIC and 3 (10%) stage IV. The procedure characteristics are listed in Table 1. The outcome of the self-reported health state is depicted in Fig. 2. At baseline, most of the patients had no to slight problems in mobility, self-care, usual activities, pain and anxiety. The median health state index was 0.80 (IQR: 0.69–0.87) and the median EQ-VAS score was 70 (IQR: 55–80). The perceived pain, anxiety and duration per treatment step

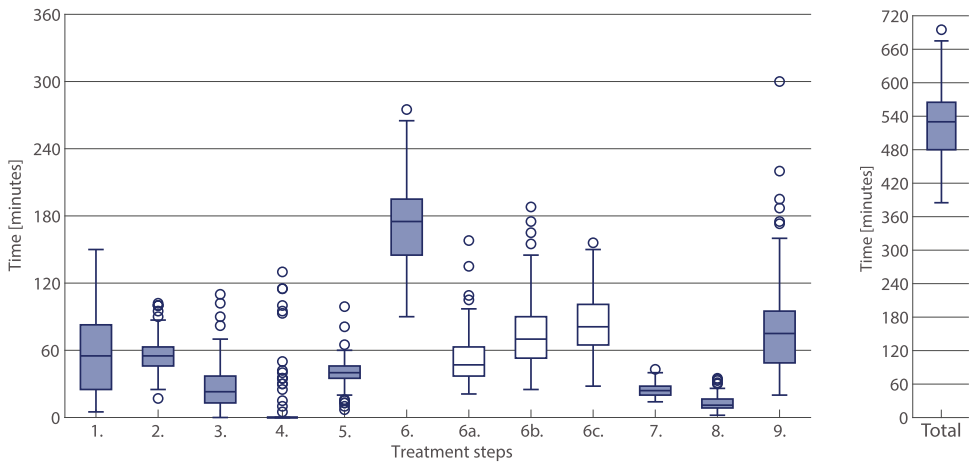

Fig. 1. Boxplots with recorded times per treatment step: 1. Preparation of implantation, 2. Applicator implantation, 3. Recovery from implantation, 4. Waiting before imaging, 5. Image acquisition, 6. Treatment planning, consisting of the partially parallel steps: 6a. Delineation organs at risk and target volumes, 6b. Applicator reconstruction, 6c. Treatment optimization, 7. Treatment delivery, 8. Applicator removal, 9. Recovery and discharge, and total. Box-plots: horizontal lines indicate median values, boxes display interquartile ranges (IQR), whiskers are 1.5 times the IQR, and circles are outliers.

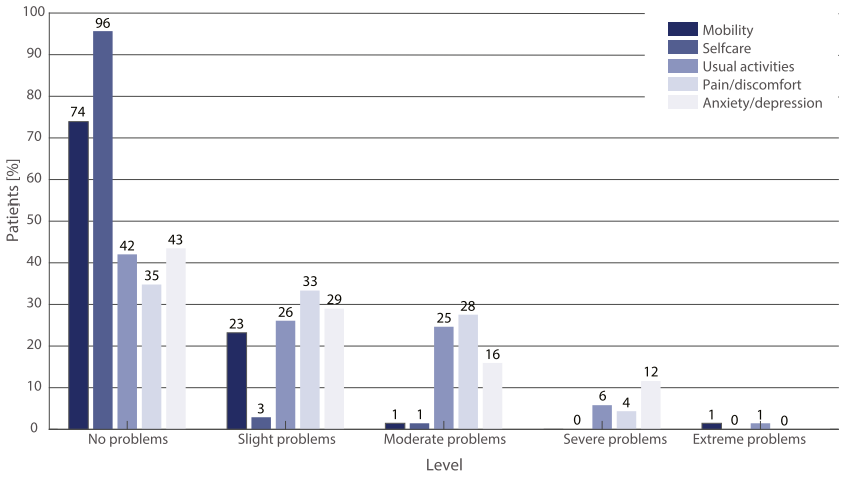

Fig. 2. Self-reported health state aspects mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

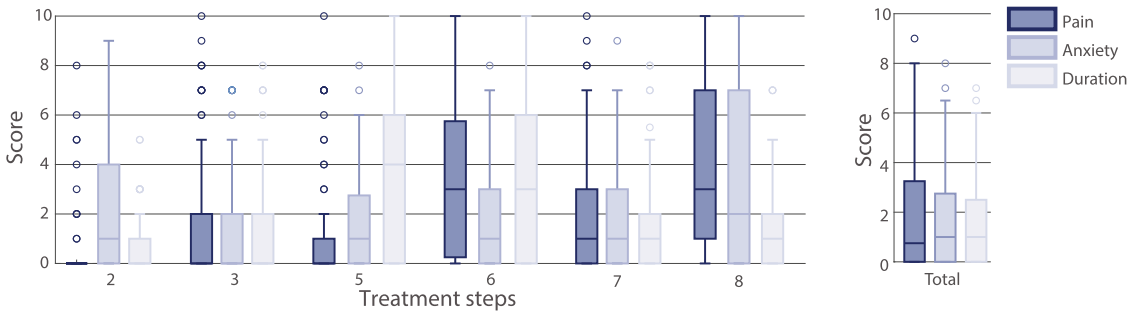

Fig. 3. Boxplots showing scores of perceived pain, anxiety, and duration for all treatment steps: 2. Applicator implantation, 3. Recovery from implantation, 5. Image acquisition (MRI/CT), 6. Treatment planning, 7. Treatment delivery, 8. Applicator removal, and total. Box-plots: horizontal lines indicate median values, boxes display interquartile ranges (IQR), whiskers are 1.5 times the IQR, and circles are outliers.

are shown in Fig. 3. The perceived pain was significantly higher during treatment planning (median: 3, IQR: 0–6, all $p < 0.001$) and applicator removal (median: 3, IQR: 1–7, all $p < 0.001$), the perceived anxiety was significantly higher during applicator removal (median: 2, IQR: 0–7, all $p < 0.0038$), and the perceived duration was significantly higher during image acquisition (median: 4, IQR: 0–6, all $p < 0.001$) and treatment planning (median: 3, IQR: 0–6, all $p < 0.001$). Patients with pain at baseline had significantly higher perceived median pain, anxiety and duration scores during treatment ($p = 0.0096$, $p = 0.0027$, and $p = 0.031$ respectively). Additionally, patients with anxiety at baseline had significantly higher perceived pain, anxiety and duration scores during treatment ($p = 0.040$, $p < 0.001$, $p = 0.012$ respectively) (depicted in Fig. 4). Limitations in activity were associated with higher perceived median anxiety scores ($p = 0.015$). Patients who received spinal anesthesia reported a significant lower overall pain score of 1 (IQR: 0–3) compared to the score reported by patients receiving general anesthesia of 5 (IQR: 3–7) ($p = 0.0025$). No significant difference between the type of anesthesia with anxiety and with duration was found. Also, no significant difference was found between the number of fractions on a day with the total treatment time and with the median perceived pain, anxiety and duration. Correlations were found between the median perceived pain and anxiety ($p < 0.001$), pain and duration ($p < 0.001$), and anxiety and duration ($p < 0.001$). No significant correlation was found between median perceived pain, anxiety and duration with the total treatment time, and with the number of needles used.

Discussion

While MRI-based IGABT for LACC has resulted in favorable outcomes, the procedure can be logistically complex and time-consuming compared to 2D image-based brachytherapy and both physically and emotionally intensive for patients (5–8,10,14–16). To guide further optimization of the IGABT workflow and enhance patient wellbeing and treatment outcomes, a better understanding of the durations and patients' experience of separate IGABT steps is required. In this study, time-action and patient experience analyses for each IGABT treatment step were done in order to give an overview of the current workflow and patient experience.

The time-action analysis determined the duration of the different treatment steps of the IGABT procedure and had

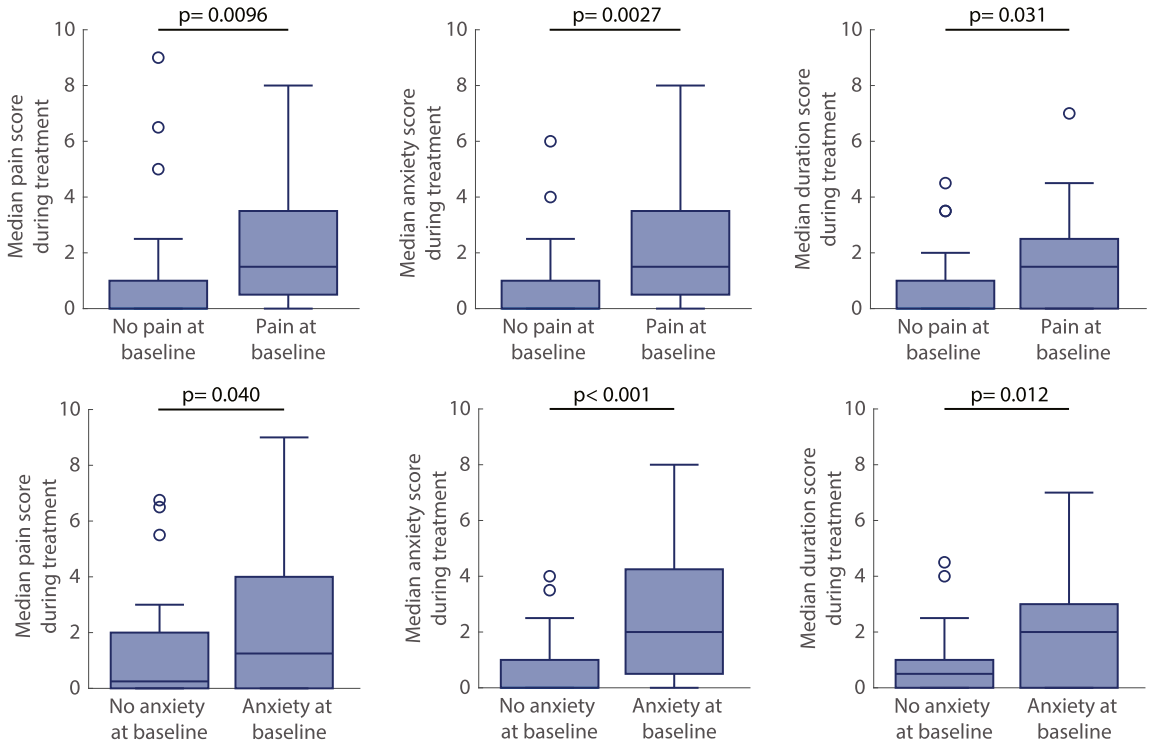

Fig. 4. The influence of pain and anxiety at baseline on the perceived pain, anxiety and duration scores during treatment.

a total median procedure time from arrival at the radiotherapy department till discharge of 530 (IQR: 480–565) minutes with a median treatment time from anesthesia to applicator removal of 354 (IQR: 319–377) minutes. Several other studies have evaluated the IGABT workflow and found shorter treatment times. Chen et al. reported a total treatment time from anesthesia to applicator removal of 219 (range: 175–336) minutes, Kim et al. found 149 (range: 112–178) minutes, and Usoz et al. found an applicator-in-place time of 179 (range: 87–311) minutes (14,15,32). Differences in procedure times reported may be explained by differences in departmental logistics (e.g., distance to MRI, waiting times), IC + IS IGABT versus IC-alone techniques, the departmental workload (average number of procedures per day), the use of alternative imaging techniques (e.g., MRI sequences) and clinical environment with training and education of new medical staff. Depending on the clinical environment, measures to shorten the overall duration may concern logistics (reduction of distances between implantation, imaging and treatment; reduction in waiting times), staffing (capacity, awareness, training), and technology (faster imaging, automation). Regarding the treatment planning step that took most of the time, several promising developments in automation are ongoing. These may shorten the time needed for contouring, reconstruction of the applicator, and planning time, such as the use of artificial intelligence for contouring and reconstruction (33–39), and automated dose planning (40). Cervical cancer incidence is particularly high in lower-middle income countries where there is still limited access to radiotherapy and brachytherapy services. The number of LACC patients requiring treatment per day is significantly higher in these high-volume departments. Although transitioning to IGABT is reported to be cost-effective, the more complex and time-consuming workflow interferes with the transition to IGABT (41–43). This highlights the importance and need for solutions that reduce the overall procedural complexity and duration.

The patient experience analysis gave insight into the perceived pain, anxiety and duration for every IGABT treatment step. Overall IGABT was associated with mild levels of pain and anxiety and a relatively acceptable duration, although some patients reported more severe symptoms and may require additional support. Significant differences in perceived pain, anxiety and duration scores per treatment step were found. The highest perceived pain scores were reported during treatment planning and applicator removal, the highest perceived anxiety scores during applicator removal, and the highest perceived duration scores during image acquisition and treatment planning. It has been previously reported that the treatment planning and applicator removal steps are the most physically uncomfortable parts of the treatment (10,12,15). The initial effect of anesthesia from applicator implantation might have largely worn off at the time of applicator removal. Additional medication can be given. However, additional medication can prolong the recovery time of the patient and elongate the total treatment time. Also alternative pharmacological or non-pharmacological interventions which can possibly lower the perceived pain and anxiety deserve

further investigation including mental support by the staff and family, education and instructions before and during the IGABT procedure, and the use of music or virtual reality during IGABT treatment (44,45). The studies of Benali et al. and Wiebe et al. found the highest anxiety score during applicator implantation and imaging, while in this analysis the highest score was found at applicator removal (11,12). A possible explanation might be differences in provided information before treatment or the pharmacological and non-pharmacological support by the medical team. Furthermore, we found that patients receiving spinal anesthesia had a significant lower overall pain score 1 (IQR: 0–3) compared to patients receiving general anesthesia 5 (IQR:3–7). The study of Locke et al. also found that patients receiving spinal anesthesia had significantly lower mean pain scores in the morning (median: 0, IQR:0–1) in comparison to patients receiving general anesthesia (median: 6, IQR: 2–8) ($p < 0.001$). Furthermore, they found that patients with spinal anesthesia had lower median opioid usage during the first IGABT treatment 23 (IQR:9–47) mg/day in comparison to general anesthesia 38 (IQR:21–71) mg/day, which was also seen in the meta-analysis of Petitt et al. (46,47). In addition, we found that patients reporting pain and anxiety at baseline had a significantly higher perceived median pain, anxiety and duration score during treatment. This pre-treatment information could help identify patients who need more support during treatment.

While prospective recording of validated outcome measures is an important strength of this study, there are several limitations that should be noted. Only single fraction procedures were included because these are more frequently performed in the department than double fraction procedures. However, double fraction procedures might interfere with the assessment of the overall workload during the brachytherapy day and its impact on the duration of treatment steps. Time-action and patient experience analyses with double fraction procedures would be interesting for future research. Furthermore, some patients received spinal anesthesia or general anesthesia, combined with additional types of analgesia and anxiolytics. The influence of the amount and type of additional analgesia and anxiolytics on the patient experience and was not included in our study. Also, comorbid psychiatric illness or addictions were not taken into account in this study. A multivariate analysis of the patient's experience with such patient and treatment variables would be of interest for future research.

Conclusion

The time-action and patient experience analyses highlight the duration of different procedure steps and their impact on the perceived pain, anxiety and duration during IGABT for LACC. Mild levels of perceived pain, anxiety and duration were found, although some patients reported more severe symptoms, specifically during treatment planning and applicator removal. Perceived pain, anxiety and duration were correlated, and pre-treatment pain and anxiety levels can help identify patients that may benefit from more supportive measures. The findings from the time-action and patient experience analyses support the prioritization of research and implementation of measures aiming to shorten the overall procedure duration, which may include logistical, staffing and technological measures and additional support for patients with more severe symptoms. Further studies should be carried out to provide more insights into the patient experience within other workflows.

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