

## Use of sedation and anesthesia in pediatric patients undergoing radiotherapy

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### Abstract

**Aim:** Radiation therapy is essential for the treatment of pediatric cancer. At least half of the children who require radiation therapy will need sedation or anesthesia. It is important to know the potential complications associated with repetitive use of sedative or anesthetic medications. The objective of the study was to describe the clinical and epidemiological characteristics of patients diagnosed with cancer at the National Children's Hospital "Dr. Carlos Sáenz Herrera" of the Costa Rican Social Security Fund, who received sedation or anesthesia during their treatment with external radiotherapy in the period from January 2016 to June 2019.

**Methods:** It is an observational, descriptive, and retrospective study of a series of cases. Pediatric patients diagnosed with cancer, who underwent radiotherapy treatment, and who required sedation or anesthesia during that intervention were included. The statistical techniques used for the qualitative variables were simple frequency tables and association or contingency tables; quantitative variables are described using central tendency and position statistics, as well as variability.

**Results:** A total of 61 patients diagnosed with cancer and receiving radiotherapy were studied. 57.4% of the patients were men. 75% of patients were 4.0 years or younger. The most frequent anatomic location of the tumor was in the central nervous system. A minority (14.5%) received radiotherapy as the only treatment. 75% of patients received 30 or fewer treatment sessions under sedation or anesthesia. Propofol was administered to 100.0% of patients in all treatment sessions. The average sedation or anesthesia time was  $67.9 \pm 28.2$  minutes. 34.4% of the patients presented respiratory or cardiovascular complications, or both, in at least one treatment session.

**Conclusions:** In pediatric patients diagnosed with cancer, the use of sedation and anesthesia during radiotherapy treatment was required mainly in young children, and in moderate frequency, the complications of the radiation therapy were temporary and usually well-tolerated, without presenting morbidity and mortality. Propofol as monotherapy turned out to have no associated complications, however, when other drugs were added, adverse effects were observed in the respiratory system, the most frequent being transient oxygen desaturation.

**Keywords:** Sedation, anesthesia, pediatrics, treatment, radiotherapy.

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**Abbreviations:** Caja Costarricense de Seguro Social, CCSS; Hospital Nacional de Niños, HNN; Central Nervous System, SNC.

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Radiation therapy is part of the cornerstone therapy in the treatment of pediatric cancer. The tumors of the central nervous system (CNS), bone sarcomas, neuroblastoma, Wilms tumor, and Hodgkin lymphoma are the most commonly treated childhood tumors.<sup>1</sup>

Radiation therapy techniques have advanced and improved considerably, although classical external beam radiation is still the most commonly used. Because of the topographic precision that these techniques require, maintaining the same position and immobility during the procedures is imperative.<sup>2</sup>

To perform pediatric radiation therapy procedures, one of the biggest logistical challenges is the patient's exposure to repeated sedation or anesthesia. It is estimated that 40-50% of children will require conscious sedation or anesthesia, especially those under 3 years of age.<sup>3,4</sup>

The ideal anesthetic agents for use in radiotherapy should show a rapid onset of action, with sedation, hypnosis, and amnesia, have a short duration of effect, show a safety profile with repeated administration together with a low risk of tachyphylaxis, minimal adverse effects, and good cost-effectiveness; The anesthetic is administered painlessly to achieve immobilization and thus maintain the patient in a single position, as well as ensuring a permeable airway in a variety of positions according to each case, all with the purpose that this intervention entails minimal interference with daily activity.<sup>5</sup> Depending on the practice in the different centers and the characteristics of the patients, moderate or deep sedation, or even general anesthesia may be chosen for the radiotherapy session.<sup>6</sup>

On the other hand, variables that may influence the complications of sedation or anesthesia for radiation therapy include the type of tumor, location, chemotherapy, type of sedative or anesthetic agent, duration of the procedure, body posture, use of an immobilizer, the patient's medical conditions, and the patient's distance from the patient.<sup>4,7-9</sup>

Following the above, the use of propofol has gained popularity due to its convenient characteristics for rapid and predictable induction, easy titration of the depth of anesthesia, and rapid recovery, which allows almost daily anesthesia.<sup>7</sup> Multiple studies have confirmed the safety of this drug, in the pediatric setting, and increased its

reliable use by specialists in the field of anesthesia and other specialties.<sup>4,7,9-16</sup> This facility for sedation or anesthesia accompanies a modification in airway management protocols in the pediatric radiation therapy setting; therefore, it is cited that most centers opt to maintain spontaneous breathing with nasocannula oxygen, positive pressure ventilation or supraglottic devices, and intravenous anesthesia.<sup>4</sup>

However, among the great diversity of patients receiving sedation or anesthesia for procedures outside the operating room, the pediatric population is the most vulnerable and at the highest risk of complications, even more so when exposed to radiotherapy in a context of hemato-oncologic morbidity.<sup>4,5,7-9</sup>

At present, at the national or regional level, no report of previous research related to this topic has been found, hence its importance and relevance; therefore, this study aims to outline the clinical and epidemiological characteristics of pediatric oncology patients treated in the Department of Hemato-oncology of the National Children's Hospital (HNN), of the Costa Rican Social Security Fund (CCSS), who received sedation or anesthesia during their treatment with radiotherapy.

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## Methods

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This study is descriptive, observational, and based on a retrospective review of clinical records. To select the study population, the following inclusion criteria were applied: age less than 13 years, with a diagnosis of cancer, who received sedation or anesthesia for the external radiotherapy procedure, both genders, without ethnicity restriction and treated between January 2016 and June 2019. Fifteen patients were excluded due to incomplete data in the records (cases with less than 50% of the required information).

The data were obtained from the clinical records of each patient and were integrated into the electronic spreadsheet, for subsequent processing of the information and descriptive statistical analysis of the study variables.

Several descriptive statistical techniques were used for the analysis of the information; for qualitative variables, simple frequency tables and association or contingency tables were used; for quantitative

variables, central tendency or position descriptors (minimum, average, maximum, quartiles) and variability (standard deviation, SD) were applied. The software used for statistical analysis of the data was Stata 14 and Microsoft Excel 2007.

This study was approved by the Scientific Ethical Committee of the National Children's Hospital "Dr. Carlos Sáenz Herrera" of the CCSS on July 14, 2017, with the assigned protocol number CEC-HNN-036-2018.

## Results

During the period analyzed and from a registry of 184 patients aged 0 to 13 years, who had an oncological diagnosis and received radiotherapy as part of their therapeutic management, it was confirmed that 76 patients (41.3%) received their radiotherapy treatment under sedation or anesthesia and of these, 15 patients were excluded due to incomplete information.

The total population for this study reached 61 patients. A total of 96.7% (59 patients) were of Costa Rican nationality and 3.3% (2 patients) were of Nicaraguan nationality. In addition, 41% (25 patients) resided in the province of San José. Distributed by sex, 35 patients (57.4%) were boys, while 26 girls (42.6%) were identified.

Of the 61 patients studied, 11.4% (7 patients) received sedation or anesthesia in 5 or fewer radiotherapy sessions, managing to complete their treatment without requiring this intervention because with time they became familiar with the procedure and the staff attending them; all patients were older than 3 years, and 71.4% (5 patients) were older than 5 years.

The mean  $\pm$  SD of the age of the patients under study was  $3.5 \pm 1.8$  years, with a range between 1.0 and 11.0 years; 75% of the patients were 4.0 years old or younger. Separated by sex, the age of the female patients was  $3.2 \pm 1.0$  years with a range between 1.0 and 6.0 years, although 75% were 3.2 years or less; the mean age of the male patients reached  $3.7 \pm 2.1$  years with a range between 1.0 and 11.0 years, with 75% extended to 5.0 years or less.

The most frequent tumor histologies in the study population were those associated with CNS neoplasms, leukemias, and neuroblastoma. The

most frequent anatomical location of the tumor was in the CNS, which occurred in 85.3% (52 patients). In addition, 45.8% (28 patients) were documented to have stage IV disease.

Concerning the interventions received by the 61 patients, 56.5% (35 patients) received chemotherapy together with surgery and radiotherapy as part of their multidisciplinary therapeutic management; while 14.5% (9 patients) received radiotherapy as the only treatment. The vast majority (98.4%) of these pediatric patients received 3-dimensional conformal external beam radiation therapy and only 1 patient received treatment with volumetric intensity-modulated volumetric arc therapy. In addition, before the start of their radiotherapy treatment, 80% of the patients participated in a simulation session and 20% (11 patients) were in 2 simulations.

When grouped according to the anatomical location of the tumor, the average number of radiotherapy sessions in patients with CNS tumor was  $22.1 \pm 13.1$  sessions, 75% of patients received 30.0 sessions or less; alternatively, in patients with abdominal tumor, it was  $16.2 \pm 9.1$  sessions, 75% of patients received 27.3 sessions or less (Table 1).

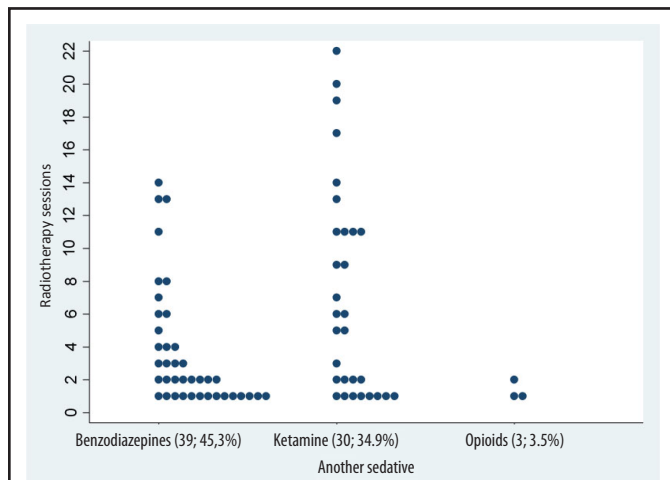
**Table 1. Distribution of patients with an oncologic diagnosis according to the anatomical site of the neoplasm and the number of radiotherapy sessions they received, January 2016 to June 2019. Department of Hemato-oncology, National Children's Hospital "Dr. Carlos Sáenz Herrera", CCSS.**

Anatomical site	Patients	Number of radiotherapy sessions	
		Average	Standard Deviation
CNS	38	22,1	13,1
Abdominal	14	16,2	9,1
Eyepiece	4	19,3	12,2
Another	5	24,0	12,0
<b>Total</b>	<b>61</b>	<b>20,7</b>	<b>12,2</b>

In all cases, patients were positioned and maintained in the supine position during the procedures; in 96.7% (57 patients) some type of immobilizer was used to maintain the position during the treatment sessions.

Concerning sedation or anesthesia, the average number of sessions performed (treatment and simulation) under sedation or anesthesia was  $20.7 \pm 12.2$  sessions/patient, 75% of patients had 30.0 sessions or less. In 90.2% (55 patients), the patient's age was the main reason for the use of a sedative or anesthetic agent during radiotherapy sessions; other reasons recorded were neurocognitive or behavioral disorders in the remaining 6 patients.

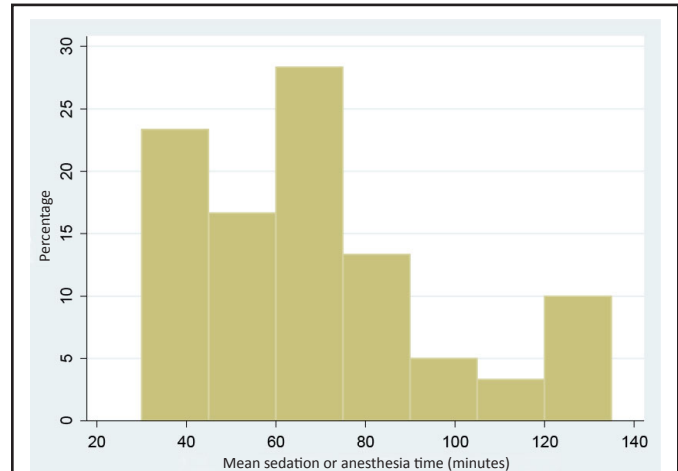
In all cases and on all occasions, sedation or anesthesia was administered by a physician specialized in Anesthesiology, without pediatric subspecialty; with non-invasive monitoring, pulse oximetry, and oxygen supply by nasocannula as part of the protocol of the Service. Likewise, parenteral propofol was the agent administered to 100.0% of patients. However, it was documented that 83.6% (51 patients) were additionally administered, in at least one session, another type of sedative or anesthetic agent (Figure 1). In 49.3% (39 patients) the agent was a benzodiazepine, in 34.9% (30 patients) it was ketamine, and in only 3.5% (3 patients) an opioid was added. In addition, in 32.3% of patients, at least in the same session, the combination of the 3 drugs: propofol, ketamine, and benzodiazepine was administered.



**Figure 1.** Distribution of patients with an oncologic diagnosis who received sedation/anesthesia according to the agent (number of patients, percentage) added to propofol and the number of radiotherapy sessions, from January 2016 to June 2019. Department of Hemato-oncology, National Children's Hospital "Dr. Carlos Sáenz Herrera", CCSS.

The average sedation or anesthesia time was  $67.9 \pm 28.2$  minutes, with a range extending from 30.0 to 135.0 minutes; 75% of patients averaged  $82.0 \pm$  minutes or less (Figure 2). In patients aged 1

to 2 years, the average sedation or anesthesia time was 68.6 minutes, while those aged 5 to 11 years averaged 58.3 minutes. In the subgroup of patients with tumors located in the CNS, the average sedation or anesthesia time was 73.7 minutes, while those with abdominal location took 59.4 minutes.



**Figure 2.** Relative distribution of patients with the oncologic diagnosis who received radiotherapy treatment according to the average time of sedation or anesthesia (minutes), during January 2016 to June 2019. Department of Hemato-oncology, National Children's Hospital "Dr. Carlos Sáenz Herrera", CCSS.

Concerning complications attributable to the application of sedation or anesthesia, these were recorded in 34.4% (21 patients), occurred in at least one session and were described as respiratory complications 19.0% (4 patients) and cardiovascular complications 14.3% (3 patients); likewise, in 14 patients (66.7%) both types of complications occurred. The respiratory complications recorded were O desaturation, suspected bronchial aspiration, and apnea; while the cardiovascular complications reported were bradycardia, arrhythmia, and arterial hypertension.

According to the therapeutic management received with cancer, complications were documented in 52.4% (11 patients) of the group that received chemotherapy and surgery in addition to radiotherapy; specifically, 7 patients presented O desaturation, and bradycardia, in 2 patients there was suspicion of bronchoaspiration, there was also 1 patient with suspicion of bronchoaspiration with apnea and 1 patient with bradycardia. On the other hand, in the 23.8% (5 patients) who underwent chemotherapy and radiotherapy, 3 patients presented O desaturation, and bradycardia, 1 patient with O desaturation, and another one with arterial hypertension; while in

the other 23.8% (5 patients) of the group treated with exclusive radiotherapy, 4 patients presented O desaturation<sub>2</sub> and bradycardia and 1 patient exhibited an arrhythmia.

When accumulating a total record of 1305 radiotherapy sessions for 61 patients, complications were documented in 4.1% (54 sessions); of which the majority, 57.4%, were complications associated with respiratory problems (O desaturation<sub>2</sub> in 28 sessions, 3 suspected bronchoaspiration, and one apnea), predominantly in patients with tumors located in the CNS; while there were 42.6% with cardiovascular problems (episodes of bradycardia in 20 sessions, one arrhythmic event and one session with arterial hypertension).

In addition, with the complications according to the agents used for sedation or anesthesia, no patient with propofol as the only medication associated complications; however, when they were additionally administered another type of sedative or anesthetic agent, at least one complication was recorded in some treatment session, predominantly those affecting the respiratory system, without being able to determine the specific causative agent given the combination of the various drugs present and that could have influenced these complications; in all cases, it was documented that the patients showed complete recovery.

The average sedation or anesthesia time of patients who associated cardiovascular complications was 89.7 min, 75% had 62.0 minutes or more on average; while the average time of patients with respiratory complications was 70.5 ± 27.1 minutes, in 75% of patients it lasted 50.8 minutes or more on average.

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## Discussion

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During the period of this study, a total of 184 cancer patients treated at the HNN who received radiotherapy were registered, of which 76 patients (41.3%) received conscious sedation or anesthesia; however, due to sufficient availability of clinical information, only 61 cases were included for the present study. According to international literature, an estimated 24-50% of children who require radiotherapy will require conscious sedation or anesthesia for this treatment.<sup>3-5,16</sup> This is not differentiated by gender, as shown in this study,

and is consistent with what has been previously described by other authors.<sup>7,16</sup>

The most prevalent tumor histologies were those associated with CNS tumors, neuroblastoma, and leukemias; the vast majority of patients underwent multiple interventions with surgery and chemotherapeutics in addition to radiation, as is to be expected with these diagnoses.<sup>1,5</sup>

It is described in the literature that the use of sedation or anesthesia for pediatric radiotherapy is primarily a function of the patient's age, it is reported that almost 100% of patients under 3 years of age require it and that at least 49% of 4-year-old children end up requiring it, similar to the results of this study.<sup>5,16</sup> So, here we report the mean age between 3 and 4 years with a mean age of 3.5 years, very comparable with the international literature mentioned.<sup>3,15,16</sup>

International studies have shown that the older the child, the lesser the use of anesthetics. In this research, it was documented that only one older patient required anesthesia, in agreement with other studies that report the use of this resource in less than 1% for children over 10 years old.<sup>16</sup>

In this research, a small number of patients received sedation or anesthesia only for the first few radiotherapy sessions as some children seem to become accustomed over time to the procedure and the staff attending them, dismissing the need for the use of medication to continue treatment. However, it is pertinent to mention that the requirement for precise positioning of patients and the use of immobilizers for radiation therapy in the pediatric population is often what brings with it the need for sedation or anesthesia.<sup>3,12</sup>

One of the most relevant studies on the evaluation of safety in radiotherapy under anesthesia was conducted at St. Jude Children's Research Hospital.<sup>7</sup> The authors reported that the position of the patients during the radiotherapy procedure under anesthesia was not associated as a risk factor for further complications, which occurred in 1.0% of patients in the prone position versus 1.5% in the supine position; furthermore, 100% of patients had a face mask, laryngeal mask or orotracheal intubation for the procedures.<sup>7</sup> Whereas here, all patients were managed with oxygen supply by nasocannula and in supine decubitus, so it is not comparable.

Properly related to the application of sedation or anesthesia, this was provided to all patients by experienced anesthesiologists, but without subspecialization in the pediatric field. In other hospitals outside our country, these procedures are performed by anesthesiologists with pediatric specialization, supported by anesthesia technicians and trained nurses.<sup>1,12</sup> However, in the literature, reviewed other specialists also describe sedation or anesthesia, who must have both the equipment and skills to respond to any emergency during the procedures.<sup>9,11,17</sup>

The mean sedation or anesthesia time in this study was 67.9 min, with no differences observed for age, previous treatment received, anatomical location, or tumor histology. This finding differs greatly from the literature, which reports average anesthesia times between 20 and 50 min.<sup>8,12,18</sup>

The importance of anesthesia times also lies in the risk of associated complications. The study conducted by Anghelescu *et al*<sup>7</sup> found statistically significant differences in the risk of complications with exposures greater than 60 minutes of sedation or anesthesia; the risk of complications was 3.28 times higher than with exposures of 31 to 60 minutes and 8.85 times higher with exposures of less than 30 minutes. In our study, the average sedation or anesthesia time was longer than 60 min in all patients with complications.

There were also no significant variations in the drugs used for sedation or anesthesia in this study concerning other studies, with propofol standing out as the drug used most frequently. Although not specific to the radiotherapy setting, a complication rate of 1.2% and 2.6% has been reported with the use of propofol in monotherapy or combination, documented from various settings outside an operating room.<sup>7,9,11,12</sup>

Also, the number of sessions under sedation or anesthesia was not found to be important to be associated with increased complications. However, it was observed that complications occurred mainly in patients with CNS primary tumor, which could be due to body position and the need for thermoplastic face masks that could compromise the airway. In other studies, more complications are also reported in procedures requiring head or neck immobilization.<sup>5</sup> In addition, complications occurred more frequently in patients who received chemotherapy and surgery in addition to radiation therapy, as documented in the literature.<sup>7</sup>

In the aforementioned study by Anghelescu *et al*,<sup>7</sup> which included more than twice as many patients as the present study, they found four risk factors for anesthesia complications in radiation therapy: the duration of the procedure, the total dose of propofol, anesthesia with propofol plus some adjuvant, and the performance of simulations. The findings of this analysis are consistent with the information, in which propofol plus adjuvant anesthesia was associated with the observation of more complications.

The limitation of the study is inherent to the design, the retrospective collection of information from the records highlighted the lack of data in the files which, however, led to the exclusion of a small number of potential participants. On the other hand, studies with larger numbers of children are needed to determine the effectiveness and safety of sedation in radiotherapy.

In conclusion, the results of this study show that sedation or anesthesia for pediatric radiotherapy is a procedure required mainly in young children diagnosed with cancer and that, with a moderate frequency, complications are transient and usually well-tolerated, without morbidity and mortality. The use of propofol as monotherapy is safe however, the addition of other drugs resulted in adverse events, highlighting transient O<sub>2</sub> desaturation among the predominant respiratory events.

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