Intraoperative Radiotherapy In Breast Cancer: Overview Of Method And Preliminary Results Of Possible Anesthetic Technique

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Citation

N Aeppli, M P Steurer, J Binder, M Fehr, A Dullenkopf. *Intraoperative Radiotherapy In Breast Cancer: Overview Of Method And Preliminary Results Of Possible Anesthetic Technique*. The Internet Journal of Anesthesiology. 2016 Volume 35 Number 1.

DOI: 10.5580/IJA.33589

Abstract

Background and Significance:

To give an overview of intraoperative radiotherapy for breast cancer treatment and report resulting anesthesia experience in the author`s institution.

Methods and Design:

Intraoperative radiotherapy (IORT) was conducted with ball applicators placed in the wound cavity and a miniature X-ray source (Intrabeam, C. Zeiss AG, Germany). Patients received Propofol target controlled infusion based general anesthesia. Standard monitoring was supplemented with bispectral index measurement. During the irradiation phase the anesthetist left the room and observed patient and monitors through leaded glass. Main outcome was the necessity to stop IORT because of necessary anesthesia related interventions.

Results:

There were 50 patients recorded. The mean procedural time encompassed 158 ± 29 min, 24.2 ± 10.2 min of which were actual radiotherapy. At the start of the radiation phase, Propofol target controlled infusion was adjusted to an effect site concentration of 2.1 ± 0.3 mg/ml (resulting in bispectral index of 40 ± 6). Patients were (re-)paralyzed with Atracurium. It was never necessary to interrupt IORT for anesthetic or patient care reasons. The irradiation phase had to be stopped once due to a technical problem and once because of a person accidentally entering the operating room. At the end of IORT, bispectral index was 43 ± 8, systolic blood pressure 99.7 ± 12.6 mmHg and heart rate 54.6 ± 8.0 min-1.

Discussion:

IORT warrants special precautions for patient and anesthetist. It is preferable for the anesthetist to physically step outside the operating room. A possible technique is presented.

BACKGROUND AND SIGNIFICANCE

Breast cancer is the most common malignant tumor in women, particularly past the age of 50 years and in industrialized countries [1, 2]. Accordingly, every effort is made to further evolve and improve therapeutic strategies. Adjuvant radiotherapy has become an important part of many treatment regimens [3, 4]. An initial radiation during the surgical procedure (intraoperative radiotherapy, IORT) can offer medical, cosmetic and logistic advantages [5-10]. IORT entails radiation exposure in the operating rooms. As a consequence, it is important for the anesthetist to know in advance what to expect with the introduction of an IORT program. This facilitates the development of a concept for the anesthetic course [11, 12].

Overview of IORT – Gynecologic/ oncological aspects

During the past 50 years, the conceptual approach to breast cancer treatment has shifted from radical mastectomy to

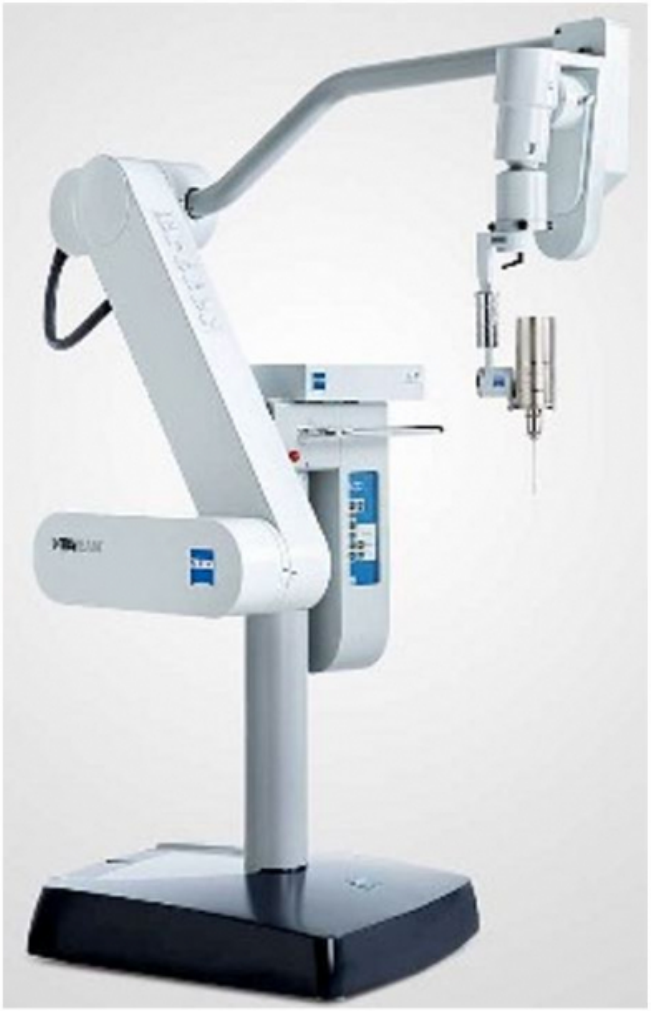
breast conserving surgery and preservation of axillary lymph nodes combined with postoperative radiotherapy and adjuvant systemic therapy [8]. The meta-analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) has demonstrated a reduction of the 10-year recurrence rate by percutaneous whole breast irradiation from 35 % to 19.3 % [13]. Loco regional recurrence was reduced from 25.1 % to 7.7 %. This resulted in a reduction of breast cancer related deaths from 25.2 % to 21.4 % after 15 years. After breast-conserving surgery for breast cancer, 90 % of local recurrences occur within the index quadrant despite the presence of multi-centric cancers elsewhere in the breast as shown by many observational studies and randomized clinical trials [14-17]. Thus, restriction of radiation therapy to the tumor bed during surgery might be adequate for selected patients.

Another argument for immediate intraoperative radiotherapy is, that any delay in delivery of radiotherapy can jeopardize its effectiveness [18, 19]. If radiotherapy is delivered intra-operatively, it would avoid a spatial miss and enable the shortest possible interval between surgical resection of the cancer and accurate delivery of radiotherapy.

The TARGIT-A trial used the Intrabeam® device (Carl Zeiss, Oberkochen, Germany; Figure 1) to provide a point source of low energy x-rays (50 kV maximum) at the tip of a 3.2 mm diameter tube that is placed at the center of a spherical tumor bed applicator [8]. After excision of the tumor, the appropriately sized applicator was positioned in the tumor bed and radiation was applied for 20-35 minutes. The surface of the tumor bed typically received 20 Gy, attenuating to 5-7 Gy at 1 cm depth. In this trial 1113 patients were randomly allocated to IORT and 1119 were allocated to postoperative external beam radiotherapy. The Kaplan-Meier estimate of local recurrence in the conserved breast at 4 years was 1.20 % (95% CI 0.53 – 2.71) in the targeted intraoperative radiotherapy and 0.95 % (0.39 – 2.31) in the external beam radiotherapy group, which was a non-significant difference. The frequency of any complications was similar in the two groups whereas radiotherapy toxicity (Radiation Therapy Oncology Group grade 3) was lower in the targeted intraoperative radiotherapy group.

Figure 1

Intrabeam device [29]



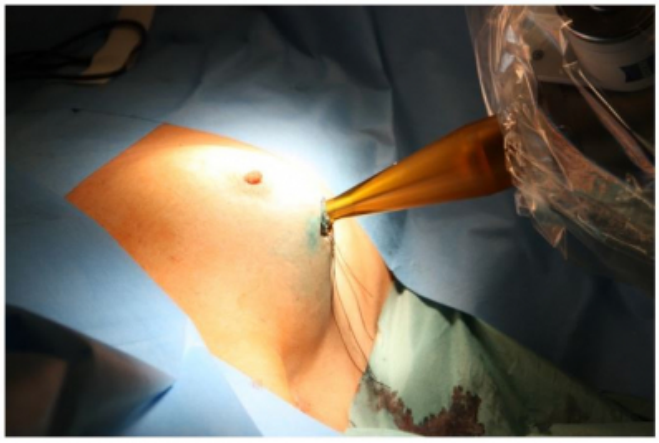
In our breast unit all patients scheduled for breast conserving therapy are evaluated for intraoperative radiotherapy at the local tumor-board. Since the largest sphere which has to be placed into the breast tissue measures 5 cm, patients with smaller resection cavities were scheduled for IORT as boost radiotherapy followed by external beam radiotherapy postoperatively. Patients eligible for the "Targit-Elderly" study were offered IORT alone without external beam radiation. For the majority of patients IORT replaced the external beam radiotherapy boost, whereas standard whole breast radiation was given.

Overview of IORT - Physical-radio-oncological aspects

The Intrabeam® X-ray source provides a spherical dose distribution with a relatively steep dose gradient, which scales as $1 / r^3$ according to experimental findings. Figure 2 shows the applicator in situ.

Figure 2

Applicator in situ



The system itself consists of a fully balanced freely movable support stand, a miniature 50 kV peak X-ray source with a gold foil anode of half value thickness at the top of a transmission tube with 3 mm diameter, in which the electron beam rotates on the envelope of a cone, a set of a 8 different spherical applicators with diameters ranging from 1.5 to 5 cm in steps of 0.5 cm, an independent control unit interfaced to a planning computer and a set of quality assurance tools [20].

Computer controlled assistance is given for tube alignment, isotropy control of the dose distribution and output verification by means of a soft X-ray ion chamber and a conventional therapy electrometer. Beam position and dose rate are internally monitored by an internal radiation monitor, measuring the backward emission of X-rays behind the gun by means of a scintillation crystal and thus controlling the deflection solenoids and correcting the treatment time for dose rate deviations. An inbuilt interlock system checks the correct entry of patient data and prevents unintended radiation exposure if the source is not correctly mounted to the support stand, an applicator is missing or mal-positioned and provides support for external controls such as door switches etc. The system is delivered pre commissioned by the manufacturer with a library of source and applicator specific dose depth data measured on a 0.1 millimeter scale and entered into the planning computer. The treatment planning system manages the patient data, monitors the course of the treatment and finally generates standardized protocols.

There is only sparse literature available on the specific anesthetic considerations surrounding IORT in breast cancer patients.

Hence, in this report, important gynecological, oncologic and physical aspects of IORT are summarized and the experience and approach to the first 50 patients undergoing IORT at the Kantonsspital Frauenfeld, Switzerland (www.stgag.ch) is reported.

METHODS AND DESIGN

After approval of the local ethics committee (Kantonale Ethikkomission Thurgau), registration with the German Clinical Trials Register (Deutsches Register Klinischer Studien, www.drks.de; DRKS00005430) and with the written consent of the patients we prospectively collected anesthesia relevant data of the first 50 patients treated with IORT in our institution.

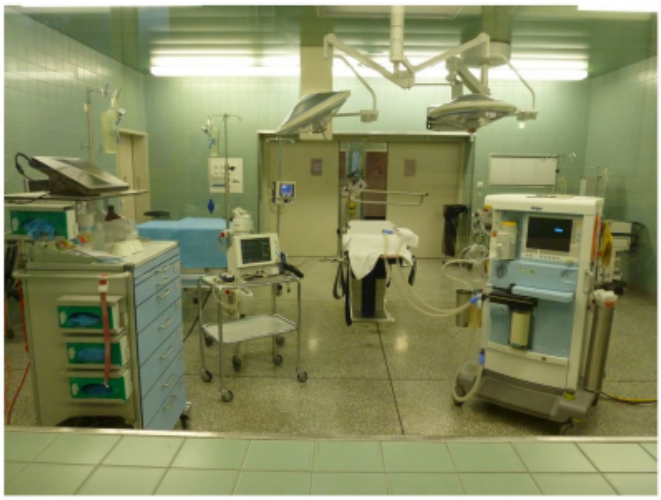
IORT – Anesthetic management

Patients received 7.5 mg Midazolam po 30 minutes before they were called to the operating rooms. The standard monitoring (ECG, non-invasive blood pressure, SpO2) was supplemented with BIS monitoring (A-2000, BIS monitoring system; Aspect Medical Systems, Norwood, MA, USA). The use of additional monitoring was based on the clinical condition of the patient. A peripheral IV catheter was inserted on the forearm of the non-operative side. According to the standard of our institution, the general anesthesia was induced with 0.1 mg Fentanyl iv, followed by 20 mg Lidocaine iv (to reduce venous irritation) and Propofol as a target controlled infusion with the initial goal of an effect site concentration of 6 mcg/ml (TCI, Schnider model; Alaris PK syringe pump; CareFusion, 305 Ltd, RG22 4BS, UK). Endotracheal intubation was facilitated by paralysis with 0.5 mg/kg Atracurium iv. The fluid maintenance and substitution was performed using Ringerfundin (B. Braun Medical AG, Sempach, Switzerland). Usual anesthesia monitoring such as end-tidal CO2- and temperature was provided. The subsequent anesthetic maintenance was achieved using Propofol via a TCI titrated to a bispectral index (BIS) target value of 40 – 60 in conjunction with remifentanil (0.05 - 0.2 mg/kg*h), or boluses of Fentanyl plus Atracurium as clinically indicated.

During the irradiation phase of the procedure, the entire staff physically departed the operating room. Both the patient and the monitors were observed thru lead-reinforced glass window (Figure 3). Before leaving the operating room, the patient was usually re-paralyzed with Atracurium and it was ensured that there was enough Propofol and Remifentanil remaining for the entire radiation.

Figure 3

View of patient and anesthesia monitoring from outside of the operating room by a lead glass pane during the irradiation phase.



After the irradiation phase the staff resumed their positions in the operating room and the surgery and anesthetic were performed in the usual fashion.

Data collection

Prospectively, we recorded patient data, process times and data of the anesthetic management as the vital monitoring values immediately before and after completion of the irradiation phase. The main outcome investigated was the need to interrupt the irradiation phase out of anesthesia related reasons. All data are presented as mean ± standard deviation or number (n).

RESULTS

The data of 50 consecutive patients were recorded (age 61 ± 10.8 years, body mass index 27.2 ± 6.9 kg/m2). 47 patients were judged to have an ASA physical status of II, the remaining 3 patients had an ASA physical status of III. Patient data are displayed in Table 1.

Table 1

Patient demographic and cancer related data. Data are mean (± standard deviation) or numbers (n).

Parameter	Unit	
Age	Years	61 (±11)
Weight	Kg	72.2 (±19.9)
Height	M	1.63 (±0.08)
BMI	Kg/M^2	27.2 (±6.9)
ASA physical status	≥ III	3
Prior chemotherapy	n	50
Prior breast surgery	n	2

The entire procedure lasted 158 ± 29 min, 24.2 ± 10.2 min of this time was used for the actual IORT (maximum duration of IORT was 55 min). At the beginning of the IORT-phase the Propofol TCI was set to 2.1 ± 0.3 mg/ml effect site concentration, resulting in a BIS-value of 40 ± 6. Thirty-three patients were re-paralyzed before the start of the IORT using 8.1 ± 7.2 mg Atracurium.

In no case was it necessary to interrupt the irradiation for anesthesia or patient safety reasons to enter the operating room. The radiation therapy had to be interrupted twice, once each for technical reasons and once because of a person accidentally entering the operating room.

At the end of IORT phase the BIS value was 43 ± 8, the systolic blood pressure 99.7 ± 12.6 mmHg and the heart rate 54.6 ± 8.0 min -1, respectively.

The comparisons of the patient monitoring values immediately before and after the IORT-phase are shown in Table 2. In only one patient (systolic blood pressure decline from 112 to 86 mm Hg), any of these parameters differed more than ± 25 % from the corresponding value at the beginning of IORT. No patient showed SpO2 readings less than 95 %, in one patient BIS value was less than 30.

Table 2

Comparison of patient monitoring values immediately before and after the irradiation phase (IORT). Data are presented as mean ± standard deviation.

Parameter	Unit	before IORT	after IORT
Heart rate	1 / min	56.0 ± 7.9	54.6 ± 8.0
Systolic blood-pressure	mmHg	100.6 ± 11.3	99.7 ± 12.6
SpO_2	%	98.2 ± 1.7	98.3 ± 1.7
BIS value	-	39.7 ± 6.1	42.7 ± 7.5

Due to the clinically insignificant variation of the values, any further statistical analysis was omitted.

DISCUSSION

The introduction of intraoperative radiotherapy (IORT) creates an unfamiliar situation for the anesthetist. In the anesthesia literature, the subject is only very sparsely covered. Therefore, an overview of this new intraoperative therapy for breast cancer patients is presented and the experience with the developed anesthesia technique to take care of the patients during the IORT reported. With the proposed technique, it was in no case necessary to interrupt the irradiation phase due to anesthesia related reasons. Apart from this, the protection of all personnel from radiation is another core aspect of this form of therapy.

Breast cancer is the most common malignant tumor in women, particularly over the age of 50 years and in industrialized countries [1, 2]. Accordingly, breast cancer therapy has hugely advanced and differentiated over time. Originally, the mastectomy was the only treatment available to the patients. Over the latter half of the last century, various treatment methods evolved and were utilized according to clinical and pathological tumor characteristics. In the 1970s the radiation therapy component was introduced and it allowed circumventing a complete removal of the affected breast in a subset of cases. The tumor extraction with tumor-free margins continued to be part of the operational regimen that included postoperative irradiation of the remainder of the gland (adjuvant radiotherapy) [3, 4].

Along with its advantages, this adjuvant radiotherapy also comes with some drawbacks. Various radiation concepts are currently under investigation to determine the best balance between maximizing tumor control, minimizing side effects and collateral damage, optimizing cosmetic results, reducing the number of required postoperative radiation sessions, and decreasing the irradiated area while increasing the daily dose [4]. The above concept can be summarized under the term accelerated partial breast irradiation (APBI). To this date, the most established APBI method is the IORT, in which, after surgical removal of the tumor, a single dose of radiation is administered to the surgical area while the patient is still under general anesthesia [7, 8, 21-23]. This immediate irradiation results in a minimal delay for the start of the radiation therapy without delays caused by wound healing and potential chemo-therapy. So a better outcome can be expected because of fewer cell repopulation. Additionally it facilitates an improved and error free localization of the tumor bed which else has to be found indirectly by means of clips etc. in the medical imaging used for the boost therapy external beam planning. Fewer side effects might be expected due to a reduced treated volume because no margins are needed [7, 10, 22, 24, 25].

In cases of early stage breast cancer and for several elderly patients even an avoidance of total breast irradiation might be possible as to be proven in TARGIT-A and E trials [8, 22, 26].

In order to take advantage of those benefits, it is essential that the patient stays completely put during the irradiation phase. With the presented technique, utilizing a Propofol-based, BIS-guided anesthesia that is supplemented by opioids this was easily achieved, even though rather low doses of muscle relaxants were used. Dosing Propofol via target controlled infusion is advantageous, as it provides stable plasma concentrations during a phase of constant and low surgical stress. Implementing the use of continuous relaxometry and administering the Atracurium as continuous infusion could possibly lead to an even higher margin of safety. In the setting of anaesthetized and paralyzed patients it is of paramount importance to systematically avoid intraoperative awareness. This holds true even more so, when considering that some of the cancer patients may be at higher risk of awareness because they are chronic pain patients that are used to opioids. It can be argued that the used TCI-concentrations for Propofol are lower than reported values for CP50 awake. However, all of our patients were premedicated with Midazolam and also received opioids, which resulted in acceptable BIS-values. When the anesthesia team leaves the operating room during irradiation, it is not possible to clinically observe the patient hence the focus on a stable anesthetic and the BIS monitoring. With our IORT setup it is actually quite easy to

stop the radiation, should it be necessary to re-enter the operating room. If that had not been the case it could have been wise to add a low dose of volatile anesthetic, to provide a higher degree of prevention of awareness. Volatile anesthetics would also provide the advantage of diminishing any need for syringe replacement during the radiation phase.

IORT leads to radiation exposure in the operating room. It is of great importance for the anesthetist to know in advance what to expect with the introduction of an IORT program, in order to develop a concept for the anesthetic approach. According to the treatment protocol of the producer of Intrabeam the breast region is covered with a radiation shielding equivalent to 0.25 mm of Pb to prevent patient and staff from residual X-rays. However, own measurements showed that the dose rate inside the operation theatre is too high to stay inside the room (approx. 120 µSv/h in 3 m distance; unpublished results). Consequently a room shielding of > 0.3 mm Pb (approximately 1.5 tenth layers) in total is recommended for a standard operation theatre of 6 x 6 meters square. Taking into account that radiation can be stopped and restarted if needed, this led to the decision, that all personnel had to leave the operation room during treatment to minimize their individual exposure and that the supervision of anesthesia as well as the physical control of the radiation source had to be done from outside using the radiation protection vitrification.

This was very easily achievable in our setting because of the window to the operating room already in place. Alternatively, a clear mobile radiation shield can be placed between the radiation source and the anesthesia team. The main objective for the anesthesia team is to provide a safe anesthetic and to closely monitor the patient throughout the entire procedure, so that an uninterrupted irradiation cycle is possible.

The literature on the anesthetic considerations surrounding IORT in breast cancer patients is very scarce. There are more publications on the topic of intraoperative radiation in the pediatric population, where such therapy has a higher incidence. But the differing sites of irradiation and operating room setups result in distinct logistical and anesthesiologic challenges [11, 12, 27, 28], mainly the inability to access the patient for some period. There have been reported cases of potentially serious incidents during the irradiation phase, such as vomiting in a sedated patient, obstruction of the endotracheal tube in the setting of a respiratory infection as well as a total lung collapse [27]. However, IORT is administered in the Operating Theatre, an area which is better staffed and equipped in comparison to a radiology suite e.g., as far as anesthesia is concerned.

We realised that it is not sufficient to just educate the staff directly engaged in a given case, since entering the operating room by uninvolved people can create a health safety hazard. The clearly visible radiation safety sign outside the doors of the operating room in itself was not sufficient to prevent such events. In the meantime we have fitted the doors to the operating rooms for IORT with additional red lights that illuminate during irradiation phases, in order to further reduce the likelihood of accidental entry by anyone.

However, it should be noted that the radiation dose that any staff members would expose themselves to when accidentally entering the operating room, is expected to be very low and without consequences. At the same time it is important to outline that the acceptable lower threshold cannot be defined and therefore the radiation exposure shall be minimized as much as possible according to the ALARA principle. ALARA stands for "as low as reasonably achievable". Should an emergency situation of any nature mandate the need to swiftly enter the operating room, the radiotherapy could immediately be interrupted when using the method and device delineated above.

There are some inherent limitations to our study. In general, the number of patients studied is surely too low to draw any universal and final conclusions about patient safety. Also, we just present one approach to the problem without comparing it to other possible proceedings, as e.g. maintenance of anesthesia with volatile anesthetics or securing the airway with a laryngeal mask.

In summary, the presented concept permits a possible approach to the anesthetic management for IORT in breast cancer patients. When initiating an IORT program, the anesthesia department has to be involved upfront. The protection of all involved employees is another important aspect.

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