Feasibility and early toxicity of intraoperative radiotherapy for breast cancer using the papillon + system: First results

Marie-Eve Chand-Fouché, Claudine Colnard, Jocelyn Gal, Daniel Lam Cham Kee, Catherine Dejean, Matthieu Gautier, Julien Feuillade, Aurélia Mana, Yves Fouché, Yann Delpech, Magali Dejode, Jean-Pierre Gérard, Emmanuel Barranger

A R T I C L E  I N F O
Keywords:
Papillon® system
Breast IORT
Brachytherapy
High dose rate

A B S T R A C T

Background and Purpose: Breast intra operative radiation therapy has been evaluated with different systems delivering 20–21 Gy with treatment times around 30 min. Papillon® Contact X-ray machine was designed to produce a 50 kVp beam with a high dose rate $>15$ Gy/minute. A pilot study with the first prototype was conducted in Nice.

Materials and methods: The inclusion criteria were age $\geq 60$ years, unifocal ductal breast adenocarcinoma $< 2.5$ cm, grade 1–2. Surgical local excision with sentinel node dissection was performed and the applicator was placed in the tumor bed after excision with a prescribed dose of 20 Gy. The main end point of the study was the doses measured with the Gafchromic films; two were located at the skin surface and two in the excision cavity. Secondary endpoints were early toxicity and relapse free survival.

Results: Between 10/2018 and 09/2019, 26 patients were included. Mean Gafchromic doses were 18.8 Gy ± 2 Gy at the south pole, 15.6 Gy ± 2.81 Gy at the equator and 2.5 Gy ± 1.67 Gy at the skin. With a median follow-up time of 12 months, no skin or subcutaneous toxicity $> 2$, no local relapse and no metastasis were observed.

Conclusion: This is the first phase II study testing the Papillon® system for breast IORT with in vivo dosimetry measurements and reassuring clinical data.

Introduction

Breast cancer is still the most commonly diagnosed cancer and the leading cause of women cancer death. Given the aging population and the increased performance of imaging, we will certainly have to face a subsequent number of newly diagnosed breast cancers, particularly among the elderly. Accelerated partial breast irradiation (APBI) could be the most suitable compromise between WBI and abstention, particularly for patients older than 65–70 years. [1,2]. Since the early 1990’s, this approach has gained great interest in the treatment of carefully selected breast cancer and several consensus have been established in the United States and Europe for patients’ selection criteria [3-6].

One of APBI technique is Intra-Operative Radiation Therapy (IORT) [7]. It can be performed using electron, and was described in ELIOT randomized trial [8]. It can also be performed with Contact X-ray Brachytherapy (CXB) using X-ray beam of 50 kVp. The largest experience was with the Intrabeam system TM (Carl Zeiss surgical, Germany) described in TARGIT trials [9,10].

Since 2018 a new system has been experimented in a phase II study in Centre Antoine Lacassagne using the Papillon + TM (Ariane medical systems, England) which can provide 20 Gy with treatment time around 1 min [11]. In order to assess the safety and efficacy of this irradiation, a phase II prospective study was conducted. We reported the results of the first 26 patients (Tables 1-3).

Materials and methods

Patient selection criteria corresponded to the “suitable” and “low-risk” groups of ASTRO and GEC-ESTRO classifications, including in situ carcinoma according to the latest update of ASTRO consensus. Eligible
patients had to be 60 years or older, with unifocal breast tumor less than 2.5 cm, ductal histologic subtypes or ductal carcinoma in-situ, low or intermediate grade, hormone receptor positive for estrogen and/or progesterone, no lymphovascular involvement, no extensive intraductal component, no clinical and radiological nodes. Local screening was performed with mammography, ultra-sound and breast MRI. All patients had breast conservative surgery with sentinel node biopsy, and intra-operative radiation therapy during the same operating time.

The Papillon-DDS is a mobile X-ray generator producing an X-ray beam of 50 kVp energy with an isotropic 310° beam angle (Fig. 1). The X-ray tube (micronode) uses a transmission tungsten anode. The system can deliver a very high dose rate of 20 Gy per minute and is battery-powered, thus allowing remote control using a mobile work station with wireless connection. The Prefectus DDS Q.A. system is made of external ions chambers measuring the output dose and beam geometry prior to use. Spherical breast applicators are made of ultem with diameters ranging from 3.5 to 5 cm. A flange is designed at the applicator top (North Pole) which is encompassing a conic volume of 50 cm³ with radius ranging from 3.5 to 5 cm. A flange is designed at the applicator top (North Pole) which is encompassing a conic volume of 50 cm³. The Papillon-DDS system can deliver a very high dose rate of 20 Gy per minute and is battery-powered, thus allowing remote control using a mobile work station with wireless connection.

As shown in Table 1, the median age of these 26 IORT patients was 73 years (range: 61–90). Breast cancer was found by systematic screening in 16 patients, breast self-exams in 6 patients, follow-up exams for 3 patients who had a history of contralateral breast cancer and one was incidental finding on a CT-scan. Pathological T stage was Tis: 2, T1a: 4, T1b: 8, T1c: 11 and T2: 1. All patients were node negative on clinical and radiological exams, but on the final pathological report, two patients were pN1. In one case, there was an extracapsular extension and the patient had an axillary node dissection, the additional nodes were negative. The two patients received post-operative irradiation to the whole breast and regional nodes. Chemotherapy (CT) was also considered in these two cases, genomic test (Endopredict test) was done and revealed high risk of relapse but only one patient accepted chemotherapy. Hormonal therapy (HT) was prescribed to 22 patients, and still ongoing in 15 cases at the last follow-up. The 4 patients who did not receive HT were 2 ductal carcinoma in situ, 1 patient with very small procedure.

The main end point of the study was the dose measured using gafchromic films positioned inside the lumpectomy cavity. The statistical hypothesis was that in 80 % of cases the dose measured should be at least 80 % of the 20 Gy prescribed dose at applicator surface. The secondary end points were early toxicity within the first 6 months, local relapse rate, metastatic relapse rate, disease free survival, overall survival, cosmetic results and patient satisfaction. Clinical examination was done two weeks after surgery and every three months with mammography and breast MRI during the first year. The toxicities were scored using CTCAE-v5, cosmetic outcome and patients’ satisfaction were evaluated by the radiation oncologist during the follow-up.

Results

Between October 2018 and November 2019, 26 patients were analyzed for the interim evaluation as per-protocol. One was not evaluable for the main end point because the two dosimeters inside the cavity were not measurable due to blood contamination.

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### Table 1

| pt | Age (y) | Comor | T clin | side | Tumour location | pT | T (mm) | pN | R0 | surg2 | EBRT | CT | HT |
|----|---------|-------|-------|------|-----------------|----|--------|----|----|-------|------|----|-----|
| 1  | 66      | +     | 1     | R    | UOQ             | 1C | 15     | 0  | R0 | No    | No   | No | No  |
| 2  | 90      | +     | 2     | L    | UMQ             | 2  | 25     | x  | R0 | No    | No   | No | n.i |
| 3  | 89      | –     | 1     | L    | UOQ             | 1C | 15     | 0  | R0 | No    | No   | No | Stopped (intolerance) |
| 4  | 67      | +     | 1     | R    | LOQ             | 1C | 13     | 1a | R0 | Yes   | Yes  | No | yes |
| 5  | 74      | +     | 0     | L    | LOQ             | 0  | 0      | R0 | No | No    | No   | n.i| n.i |
| 6  | 64      | –     | 1     | L    | LOQ             | 1B | 9      | 0  | R0 | No    | No   | No | Stopped (intolerance) |
| 7  | 84      | +     | 1     | R    | LQ              | 1A | 3      | 0  | R0 | No    | No   | No | n.i |
| 8  | 63      | +     | 1     | L    | UOQ             | 1C | 15     | 0  | R0 | No    | No   | Yes| yes |
| 9  | 79      | +     | 1     | L    | UMQ             | 1C | 20     | 0  | R0 | No    | No   | No | yes |
| 10 | 75      | +     | 1     | L    | UOQ             | 1B | 8      | 0  | R0 | No    | No   | No | Stopped (intolerance) |
| 11 | 62      | –     | 0     | L    | UMQ             | 1B | 7      | 0  | R0 | No    | No   | No | Stopped (intolerance) |
| 12 | 70      | +     | 1     | L    | UOQ             | 1A | 5      | 0  | R0 | No    | No   | No | Stopped (intolerance) |
| 13 | 73      | +     | 1     | L    | UOQ             | 1C | 11     | 0  | R0 | No    | No   | No | Stopped (intolerance) |
| 14 | 87      | –     | 1     | L    | UOQ             | 1B | 10     | 0  | R0 | No    | No   | No | yes |
| 15 | 69      | –     | 0     | R    | UOQ             | 1B | 9      | 0  | R0 | No    | No   | No | No |
| 16 | 61      | CBC   | 1     | R    | UOQ             | 1A | 4      | 0  | R0 | No    | No   | No | n.i |
| 17 | 73      | +     | 1     | L    | UOQ             | 1B | 9      | 0  | R0 | No    | No   | No | Stopped (intolerance) |
| 18 | 74      | +     | 0     | L    | UQ              | 1A | 18     | 0  | R0 | No    | No   | No | No |
| 19 | 72      | –     | 0     | L    | UQ              | 1C | 19     | 0  | R0 | No    | No   | No | Stopped (intolerance) |
| 20 | 76      | –     | 0     | L    | UQ              | 1A | 5      | 0  | R0 | No    | No   | No | Stopped (intolerance) |
| 21 | 73      | –     | 1     | R    | UOQ             | 1C | 20     | 0  | R0 | No    | No   | No | Stopped (intolerance) |
| 22 | 73      | –     | 1     | L    | UMQ             | 1B | 7      | 0  | R0 | No    | No   | No | No |
| 23 | 71      | +     | 1     | L    | UOQ             | 1C | 16     | 0  | R0 | No    | No   | No | yes |
| 24 | 86      | + and CBC | 2 | L    | LOQ             | 1C | 8      | 0  | R0 | No    | No   | No | yes |
| 25 | 73      | +     | 1     | L    | UOQ             | 1C | 13     | 0  | R0 | No    | No   | No | yes |
| 26 | 61      | +     | 1     | R    | UOQ             | 1C | 13     | 0  | R0 | No    | No   | No | yes |

y: year Comor: comorbidity; R: Right; L: Left; Surg 2: second surgery; CBC: contralateral breast cancer previously treated; EBRT: external beam radiation therapy; CT: chemotherapy; HT: hormonal therapy; n.i: not indicated; UOQ: upper outer quadrant; UMQ: upper medial quadrant; LOQ: lower outer quadrant; LMQ: lower medial quadrant; Surg 2: second surgery; EBRT: External Beam Radiotherapy; CT: chemotherapy; HT: hormonotherapy.
tumour (3 mm) and one 90-year-old patient with significant comorbidities. Hormonal therapy was refused by three patients and was discontinued in four cases because of side effects.

The IORT was performed in these 26 patients without any difficulty delivering a 20 Gy dose prescribed at the applicator surface. The applicator diameter was 3.5 cm in 13 cases, 4 cm in 6 cases, 4.5 cm in 3 cases and 5 cm in 4 cases. Times of irradiation for applicator 3.5, 4, 4.5 and 5 cm were 39, 58, 83 and 112 s respectively. The applicator was selected to have the closest contact between the applicator surface and the whole surgical cavity. Quality of applicator positioning was estimated by the radiation oncologist and the surgeon excellent or good in respectively 90 % and 10 % of the cases (Table 2).

Depth dose profiles (DDP) are shown in Fig. 2 for all applicator sizes. They were normalized to the surface of the applicator at the prescription dose of 20 Gy. Depth dose measurements increase with increasing applicator size. Doses measured at different depths between 2 and 50 mm are summarized in Table 3. The dose decreases to around 24–36 % of the surface dose at 1 cm depth and to 9–16 % at 2 cm depth, depending on the size of the applicator. Dose gradients are steeper for smaller applicators.

For the 26 patients, dose measurements for skin doses vary between 0.2 Gy and 7.2 Gy. The mean measured skin dose is 2.5 Gy ± 1.67 Gy, independently of the size of the applicator. Dose measurements are between 13.4 Gy and 21.7 Gy at the South Pole and between 11 Gy and 22 Gy at the Equator of the applicator. The mean measured dose is 18.8 Gy ± 2 Gy at the South Pole and 15.6 Gy ± 2.8 Gy at the Equator (Table 4).

IORT was delivered with applicators ≤ 4 cm for 19 patients and with applicators ≥ 4.5 cm for 7 patients. When comparing the doses using small applicators (3.5 and 4 cm) and large applicators (4.5 and 5 cm), there was a trend favoring large applicators. Doses above 16 Gy at the South Pole were seen in 15 cases (83.3 %) with small applicators versus 7 cases (100 %) with large ones. Doses above 16 Gy at the Equator were seen in 7 cases (38.7 %) with small applicators versus 4 cases (57.1 %) with large ones.

The median follow-up time was 12 months. Acute toxicity was observed for 7 patients: 2 skin toxicities grade 1 (erythema), 1 breast seroma grade 1, 1 skin edema grade 2, and 3 hematomas (2 grade 1 and 1 grade 2). No patient required any reoperation or hospitalization for any toxicity. Hospital stay was one day for 20 patients and two days for six. Two patients received a complementary whole breast and regional nodal irradiation at a dose of 50 Gy/25 fr/ 5 weeks and acute toxicities were grade 2 or less. Chronic toxicities were skin toxicities grade 1 for 2 patients: 1 telangiectasia, 1 hyperpigmentation. No patients had fibrosis > grade 2 nor breast pain > grade 2. Cosmetic results were scored as good to excellent for 24 patients, bad for 2 patients: one had a large hematoma and one had psychological disorders and difficulties to accept the scar. Patient satisfaction was estimated good to excellent in the same 24 cases. No local relapse, metastasis or death was observed.

Discussion

IORT is an interesting option for low-risk breast cancers. With the new Papillon + tm system, the irradiation can be delivered during a very short time, around one minute. This additional benefit is important for all the multidisciplinary team who is mobilized in the operating room, and mostly for the patient who does not need a prolonged anesthesia for this procedure. Our study has a short follow-up but the results are encouraging with no toxicity > grade 2. They are in accordance with other published results. We did not observe local relapse nor metastasis, but the number of patients is small and the follow-up is too short to draw significant oncological conclusions. We can also notice that more than a third of patients declined or early stopped endocrine therapy, which can significantly affect expected results. Maybe favorable histologic

| Applicator diameter [mm] | Depth [mm] | SouthPole (Gy) | Equator (Gy) | Skin 1 (Gy) | Skin 2 (Gy) |
|--------------------------|------------|----------------|--------------|------------|------------|
| 35                       | 0          | 20             | 20           | 20         | 20         |
| 40                       | 14.3       | 15.0           | 15.6         | 15.9       |            |
| 45                       | 9.0        | 10.1           | 11.0         | 11.6       |            |
| 50                       | 7.0        | 7.6            | 6.5          | 7.2        |            |
| Depth doses for all applicator sizes at different depths ranging from 2 mm to 40 mm. The profiles were normalized to the prescription dose of 20 Gy at the surface of the applicator.

Table 3

| patient | Applic Diam (cm) | Irradiation time (s) | South Pole (Gy) | Equator (Gy) | Skin 1 (Gy) | Skin 2 (Gy) |
|---------|------------------|-----------------------|-----------------|--------------|-------------|-------------|
| 1       | 3.5              | 39,00                 | 15              | 13           | 2.1         | 1.5         |
| 2       | 3.5              | 39,00                 | 19              | 12.5         | 0.4         | 1           |
| 3       | 3.5              | 39,00                 |                |              |             |             |
| 4       | 3.5              | 39,00                 | 19,2           | 14.4         | 0.4         | 0.2         |
| 5       | 4.0              | 58,00                 | 18              | 15           | 3.9         | 4.7         |
| 6       | 3.5              | 39,00                 | 20.3           | 15.2         | 7.2         | 3.9         |
| 7       | 4.0              | 58,00                 | 19.8           | 13.8         | 4.2         | 4.9         |
| 8       | 4.0              | 58,00                 | 18.6           | 16           | 1.7         | 0.5         |
| 9       | 4.5              | 83.00                 | 19.3           | 16.2         | 2.1         | 4.7         |
| 10      | 5.0              | 112.00                | 19.1           | 15.4         | 2           | 6.3         |
| 11      | 4.5              | 83.00                 | 18.9           | 16.2         | 2.8         | 2.3         |
| 12      | 3.5              | 39.00                 | 19.9           | 14.3         | 1.3         | 1.3         |
| 13      | 3.5              | 39.00                 | 21.2           | 13           | 0.6         | 0.7         |
| 14      | 3.5              | 39.00                 | 21.1           | 18.9         | 0.4         | 0.7         |
| 15      | 4.5              | 83.00                 | 21.7           | 18.7         | 2.2         | 7.2         |
| 16      | 4.0              | 58.00                 | 18.6           | 13.1         | 4           | 1.8         |
| 17      | 3.5              | 39.00                 | 13.4           | 14.4         | 2.4         | 1.84        |
| 18      | 5.0              | 112.00                | 16             | 13           | 3.9         | 3           |
| 19      | 3.5              | 39.00                 | 20              | 11           | 1.7         | 0.3         |
| 20      | 3.5              | 39.00                 | 19.2           | 12           | 3.4         | 3.7         |
| 21      | 4.0              | 58.00                 | 21.1           | 18.2         | 2.1         | 2.9         |
| 22      | 5.0              | 112.00                | 20.1           | 21           | 2.2         | 1.3         |
| 23      | 4.0              | 58.00                 | 18.5           | 16.3         | 2           | 4.4         |
| 24      | 3.5              | 39.00                 | 19.1           | 23           | 2.8         | 1.8         |
| 25      | 5.0              | 112.00                | 20              | 18.3         | 1.4         | 2.6         |
| 26      | 3.5              | 39.00                 | 19              | 18.7         | 3.2         | 3.5         |
parameters have negatively impacted the motivation of both the patient and the physician to continue endocrine therapy for five years. IORT is already a therapeutic de-escalation and so, we have to remain cautious about endocrine therapy omission or discontinuation.

In TARGIT trial, 3451 patients were randomized between IORT 20 Gy with contact X-ray beam and whole breast irradiation (WBI). The IORT patients were treated either during the same procedure “immediate or pre-pathology group”, or during a second surgery “delayed or post-pathology group”. After a median follow-up of 2.5 years, the local relapse rates were 1.3 % for IORT groups and 3.3 % for WBI group [10]. Vaidya and colleagues have just published the long term results of the whole cohort [14]. With a median follow-up of 8.6 years, there were no statistically significant difference for local recurrence free survival, disease free survival, overall survival; and mortality from other causes was significantly lower for TARGIT IORT group.

The German team of TARGIT published the results of highly selected breast cancers with patients aged 50 years-old or more, unifocal ductal carcinomas T1N0, treated with “immediate” IORT. With a follow-up of 8.5 years, they observed no local relapse [15].

Some French centers have now quite a long experience of INTRABEAM system. The Montpellier Department of radiation oncology conducted a monocentric prospective observational study: patients aged 60 years or more, with unifocal non-lobular carcinomas ≤ 2 cm, SBR < grade 3, N0, ER +. They reported the results of the first 200 patients treated with IORT. With a median follow-up of 53.4 months, the local relapse was 2.5%, the patient satisfaction was excellent for 86.9 % and cosmetic results was considered by patients and physicians as good—very good for a large majority of patients: 89.4 % and 97.3 % [16]. A retrospective analysis was recently published by Tallet and colleagues: 676 highly selected patients treated with breast conserving surgery and IORT, with a median follow-up of 54 months, the 5-year local recurrence rate was 1.7 % and there was no grade 3 toxicity [17].

A limitation of IORT is actually the lack of image-based treatment planning, without which we are unable to anticipate the radiation dose delivered to the tumoral bed and to the adjacent organs such as the skin. A very small number of studies have reported in vivo dosimetry performed inside the excision cavity and our study is the first one testing the Papillon +™ system for breast IORT.

Gafchromic EBT3 films have been chosen for quality control and in-vivo dosimetry due to their high spatial resolution, their decreased room light sensitivity and their near tissue equivalence. They can also easily be cut into small pieces and placed into a sterile envelope [18].

The mean skin dose in this study was 2.5 Gy (0.2 to 7.2 Gy) and was in good agreement with other skin doses measured in similar situations. In a Korean phase 2 trial, radiation dose delivered to the skin was measured by optically stimulated luminescence dosimeter (OSLD) during IORT as a boost (20 Gy) for 82 patients [19]. The mean dose was 1.91 Gy (range, 0.2 to 7.2 Gy).

| Applicator diameter [mm] | Mean Dose [Gy] | Standard deviation [Gy] |
|-------------------------|----------------|-------------------------|
|                         | South Pole     | Equator                 | South Pole | Equator | Skin     |
| 35                      | 18.74          | 15.80                   | 2.06       | 2.22    | 2.69     |
| 40                      | 18.53          | 14.80                   | 2.71       | 1.88    | 3.56     |
| 45                      | 20.23          | 16.13                   | 3.28       | 1.09    | 1.65     |
| 50                      | 18.45          | 16.10                   | 3.01       | 1.51    | 2.09     | 1.13      |
intrabeam iort [21]. the average skin dose was 1.18 Gy, ranging from 0.17 to 4.77 Gy. our clinical results are reassuring because the main difference between the Papillon + ™ unit and other 50 kV systems is the dose rate which is 20 times higher using Papillon+™ and could be responsible for more skin (or other tissues) toxicity. a very close surveillance protocol was implemented in this study and so far with a median follow-up time of 12 months, no grade > 2 toxicity of any form was reported. Moreover, measured skin doses did not depend on the applicator size. the non-irradiated volume at the “north pole” of the applicator may provide a better skin sparing.

at the south pole, we found a mean dose of 18.82 Gy (range 13.4 to 21.2 Gy). at the equator, the mean dose was 15.65 Gy (range 11 to 18.9 Gy), and so we did not reach the main endpoint which was 80 % of the prescribed dose. the dose is homogeneous around the equator of the applicator with an estimated homogeneity less than 5 % and a relative standard deviation up to 3 %. due to the geometry of the micro-node, the dose drops close to the north pole of the applicator. as a result, along the meridians, the homogeneity is below 8 % and the relative standard deviation of the dose distribution is less than 4 %. according to the manufacturer, the expected uncertainty is less than ± 3 % in sensimetric response from mean and the dose uniformity is better than ± 2 % when using filmqaPro and a triple-channel dosimetry protocol as the one that was exploited for this study [22]. the expected variation in dose measurements due to film dose response is thus likely to be small compared to other experimental uncertainties.

dose gradients could be observed on most measurements in the equator region, so it may be assumed that the films were partly displaced during the tightening of surgical strings before irradiation. the close contact of the gafchromic film with the applicator surface was probably better on the south pole than on the equator because of non-homogeneity in the surgical cavity. the excision cavity was made of mammary fatty and glandular tissues which are of irregular surface and possibly at the equator level, despite the surgeon purse string, the dosimeter can be positioned some distance away from the applicator surface (in a breast tissue defect) as shown on fig. 3. such a gap is possibly larger at the equator level than at the south pole. (fig. 3) the mean dose measured at the equator shows a decrease of 20–28 % of the prescription dose, depending on the applicator size. according to the papillon + depth dose profiles, these measurements correspond to a dose at 1–2 mm from the applicator surface that could be explained by air gaps and/or a mispositioning of the films. the dose expected at 2 mm depth is between 14.3 and 15.9 Gy for an applicator size of 3.5 to 5 cm, respectively. the error on the measured dose was generally more important for smaller applicators due to the steeper dose gradients they generate. we can already assume that the use of a larger applicator size would have overcome these problems at the equator. of course, we have to try to be even more cautious about the choice of the applicator. this could also lead to the conclusion that we should imagine an applicator with a different shape, wider than it is high, providing greater capacity to cover the whole surgical cavity.

in breast iort, the standard prescribed dose is 20 Gy. using electron, this 20 Gy dose is homogeneous in a volume close to 100 cm³. using 50 kV X-ray beam the situation is very different with an inhomogeneous dose delivered in a much smaller volume close to 40 cm³ which means that at 1 cm from the applicator surface, depending on the applicator diameter, the dose is between 4 and 6 Gy. with such a dose distribution it is not known if it is the maximum, minimum at 1 cm or mean dose which is relevant to achieve local control. if the maximum dose can be reduced by 10 to 40 % for reasons discussed previously, the mean dose and the minimum dose at 1 cm depth are kept within 10 % variation or less. the choice of the optimal dose to achieve local control using 50 kV X-ray IORT remains an open question.

fig. 3. schematic artist representation of the dose measured using gafchromic film. it can be seen that the dark blue area (receiving between 20 and 11 Gy) is irregular (irregular mammary gland cavity after tumor local excision). the dose measured close to the applicator, depending on this irregularity and close contact of the gafchromic film, can vary between 20 Gy (south pole) and 13 Gy (equator right). this mammary gland surface dose inhomogeneity has no impact on the dose between 5 and 10 mm depth (clear blue area) which is always between 10 and 7 Gy. the mean dose to this volume of tissue is around 12 Gy with little variation for the same applicator diameter. this mean dose is larger with the 4.5 cm diameter applicator than with the 3.5 cm. in this sketch the applicator diameter is 4 cm. the irradiated volume (dark and clear blue) is close to 40 cm³ (14 % of the sphere on the north pole receiving no dose). the two gafchromic films positioned at the skin surface close to the surgical incision are at > 1 cm from the applicator surface they receive a small dose close to 2 or 3 Gy in one minute. (for interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

our study was stopped pre-maturely before the end of inclusion because we could not meet the 80 % prescription dose at the equator inside the surgical cavity. the end point of the present study was met when measuring the dose on the south pole of the cavity (mean dose 18.8 Gy) but not on the equator (mean dose 15.6 Gy). it was probable that the dose level constraint chosen at the equator in this protocol was too stringent to be met. a more clinically relevant end point such as early toxicity would be used in the next feasibility study.

conclusion

our phase II study is the first one testing in human the Papillon +™ system for breast IORT with in vivo dosimetry performed inside the excision cavity. it was stopped as the main end point was not met. nevertheless, IORT using Papillon +™ seems a safe procedure and a new trial has been launched (September 2021) with clinical toxicity as the main end-point. with longer follow-up, we expect breast IORT delivered in one minute versus 20 to 30 min will provide similar overall clinical outcomes, and patients’ greatest satisfaction.

declaration of competing interest

Dr P-J P Gérard declares he is medical advisor without any financial conflict for Ariane and Clerad.

the other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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