

A New Intraoperative Gamma Camera for the Sentinel Lymph Node Procedure in Breast Cancer

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Abstract. *Aim: This study aimed at evaluating the performance of an intraoperative gamma camera, named CarolIReS, to detect axillary drainage and to assess the removal of sentinel lymph nodes (SLN) in breast surgery. Patients and Methods: SLN biopsy was performed on 25 patients and the CarolIReS camera was used preoperatively to localize SLNs. During surgery, individual removal of SLNs was performed using a gamma probe and their activity was measured with a gamma ray counter. At the end of surgery, the CarolIReS camera was used again to check the quality of surgery which was followed by surgical excision for remaining SLNs. Results: The detection efficiency of the CarolIReS camera was 2.2 cps/kBq for ^{99m}Tc activity in SLNs. In one case, it allowed the detection of a residual SLN with a low activity (0.5 kBq) which was massively metastatic. Conclusion: Intraoperative cameras could be used to improve the efficiency of the SLN procedure.*

In breast cancer, the traditional staging procedure, axillary lymph node dissection (ALND), carries a significant risk of side-effects, including neuropathy, seroma formation, shoulder dysfunction and pain. Moreover, the incidence of postoperative lymphoedema ranges from 6% to 30% (1). Consequently, ALND is being replaced in selected patients by the sentinel lymph node (SLN) biopsy, with the aim of significantly reducing physical and psychological morbidity (2). The SLN is the first node in which lymphatic drainage and cancer cell colonisation occur (3, 4) and the SLN procedure is now widely used in the staging of breast cancer patients (5).

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Key Words: Breast cancer, CarolIReS, intraoperative gamma camera, lymphoscintigraphy, sentinel lymph node.

One main pitfall of this procedure is failure to visualize SLN, which would underscore the tumour staging, leading to suboptimal treatment or lymph node recurrence (5). A meta-analysis of approximately 70 published trials on the use of SLN biopsy has revealed a false-negative rate of 8.4% (6). However, according to international criteria, this false-negative rate should be less than 5% (7). For example, the American Society of Breast Surgeons recommends a rate of SLN identification of 85% with a false negative rate of 5% or less in order for ALND to be abandoned (8). For this reason, the technique of SLN detection needs to be improved.

The classic SLN procedure uses preoperative lymphoscintigraphy, blue-dye injection and an intraoperative gamma probe. In the USA, many centres no longer perform routine lymphoscintigraphy (9) and use it only in selected cases, such as those of medially located tumours. The aim of preoperative lymphoscintigraphy is to demonstrate drainage to axillary and non-axillary nodal areas. In order to localize this drainage and to assess the quality of surgery, intraoperative gamma cameras are being tested. These systems are based on two types of detector materials, semiconductors, such as cadmium zinc tellure (CdZnTe) (10-12) and cadmium tellure (CdTe) (13), or scintillating crystal using sodium-doped cesium iodide (CsI:Na) (14) or thallium-doped sodium iodide (NaI:Tl) (15). For most of these devices, the field of view (FOV) is too small to map the lymph node areas in their entirety (axillary, internal or susclavicular). In addition, the choice of semiconductor materials as photodetector leads to poor sensitivity and long image acquisition time. The published results lack systematic clinical validation (10-15), with the exception of the Motomura Study which included 29 patients (16).

Consequently, the Institut Pluridisciplinaire Hubert Curien (IPHC) has developed an intraoperative gamma camera named CarolIReS (17), based on a single fast decay time inorganic scintillating crystal, allowing good detection efficiency and short image acquisition time.

The aim of this study was to evaluate the performances of the CarolIReS camera in assessing the axillary drainage of breast tumours and the surgical removal of SLNs in a prospective series of 25 patients with breast cancer justifying SLN biopsy. In addition, the possible correlation between the activity and the size of the metastatic SLNs was also studied.

Patients and Methods

Patients. Twenty-five patients with infiltrative breast cancer or ductal carcinoma *in situ* (DCIS), diagnosed preoperatively by core biopsy, were enrolled in the study after approval and informed consent (18). The study (ClinicalTrials.gov identifier: NCT00357487) was approved by Local Research Ethics Committees and reviewed in accordance with the precepts established by the Helsinki Declaration. None of the patients had undergone chemotherapy, locoregional radiotherapy, or prevalent axillary lymph node. After surgery, all patients were submitted to a clinical, radiological (mammography and ultrasound) and biological [cancer antigen (Ca) 15-3] follow-up twice a year.

CarolIReS camera. The prototype of the CarolIReS camera comprises of a parallel lead collimator, a 2 mm-thick single fast decay time inorganic scintillating crystal (GSO:Ce: cerium-doped gadolinium silicate), a multichannel photomultiplier tube (H8500; Hamamatsu Corp. Hamamatsu City, Japan), fully dedicated electronics and software treatment for image reconstruction (17). The FOV of the device is 50x50 mm². The data acquired by the gamma camera are displayed on a screen as a projection with a pixel size of 1x1 mm². The detection efficiency of the system is 2.2 cps/kBq with a spatial resolution of 10 mm for a point source located at 50 mm from the collimator.

CarolIReS probe. The CarolIReS probe combines a fast decay time yttrium aluminium perovskite activated by cesium (YAP:Ce) crystal, as the ^{99m}Tc 140 keV γ -ray detector by photoelectric effect and a Hamamatsu H3164-10 photomultiplier tube for scintillation photon detection (19). The detection head of this probe consists of a cylindrical aluminium-coated crystal (4 mm diameter, 12 mm length), surrounded by a 3 mm-thick moveable tungsten (W) shield which acts as a two-position collimator. The closest collimation is maintained by a thumb-wheel which, by way of a spring, returns to the maximum solid angle aperture when released. The electrical signal produced by the photomultiplier is analysed on a dedicated electronic board, following its charge integration by an analog to digital converter, and then transformed into a proportional frequency sound signal. At a distance of 10 mm, the spatial resolution-calculated as the full width at half maximum (FWHM), is equal to 13.7 mm and 8.5 mm for open and closed collimation positions, respectively. The mean sensitivity is 13.5 cps/kBq for an effective detection head area of 12.5 mm².

Gamma ray counter. The detector is based on a YAP:Ce crystal cylinder (20 mm diameter, 10 mm thickness) coupled to a photomultiplier tube. The 26% geometrical efficiency of the counter has been estimated by simulation (19) and validated with radioactive standard and several experimental SLN activities. The activity is measured with a 5% error. This correction factor is applied to obtain the absolute SLN activity after resection.

Table I. Patient characteristics.

Number of patients	25
Unilateral BC	23
Bilateral BC	2
Treatment of the 27 tumours	
Axillary clearance	8 (30%)
Conservative surgery	17 (63%)
Mastectomy	10 (37%)
Tumour type	
Ductal	17 (63%)
Lobular	1 (4%)
Mucinous	2 (7%)
Tubular	1 (4%)
DCIS	6 (22%)
Tumour size of the 21 infiltrative BC [mean (SD)mm]	13 (5.6)
Grade of the 21 infiltrative BC	
Low	9 (43%)
Intermediate	7 (33%)
High	3 (14%)
ND	2 (10%)
Lymphovascular invasion	1 (5%)
Hormonal factors of the 21 infiltrative BC	
ER +	13 (62%)
PR +	10 (48%)
C-erb B2 +	1 (5%)

BC, Breast cancer; DCIS, ductal carcinoma *in situ*; ND, not determined; ER, oestrogen receptor; PR, progesterone receptor; Data are presented in means (SD), or numbers (percentage).

Procedures in surgery. The SLN procedure was initiated 18 hours before surgery using a preoperative injection of colloidal rhenium sulphur and technetium (0.4 ml, 20 MBq of Nanocis®; CIS Bio International, France) at the four cardinal points in the subareolar area. Lymphoscintigraphy (Hélix®, Elscint, Haifa Israël) was obtained 3 hours after the injection. Immediately before surgery, the axillary drainage was checked using the CarolIReS camera. Due to the small FOV (50x50 mm²) of the camera, four images were obtained with each image acquisition lasting 2 minutes. During surgery, the search for radioactive nodes was performed using the CarolIReS probe (19). In order to evaluate the CarolIReS camera sensitivity, the activity of the removed SLNs was measured immediately after their resection by a gamma ray counter and they were then submitted to pathological analysis with frozen section. The long and short SLN axes were measured and the SLN size was defined as the ellipsoidal cross-sectional surface: ($\pi \times$ long axis \times short axis)/4. After SLN removal and during the pathological analysis, the axillary area was once again checked using the CarolIReS camera (4 images) followed by a further surgical excision in the case of remaining SLNs.

If the pathological analysis diagnosed a metastatic SLN, complete ALND was immediately performed. In the case of negative SLN, serial sections and detection of cytokeratine (AE1/AE3; Dako, Zymed, CA, USA) were performed during standard pathological analysis. Macrometastases were defined as clusters of cancer cells ≥ 2 mm, micrometastases as clusters of cancer cells ≥ 0.2 mm and < 2 mm, and isolated cancer cells as clusters of cancer cells < 0.2 mm. ALND was performed in cases of macro- or micrometastases.

Results

Patient and tumour characteristics and breast surgery. Data are summarized in Table I. The mean age of the 25 patients was 55 (29-80) years and their mean weight was 62 kg (standard deviation, SD, 13 kg). Twenty-three patients were treated for unilateral breast cancer and two for bilateral breast cancer (13 right breasts and 14 left breasts, representing 27 cases). There were 21 infiltrative breast cancers and six DCIS. DCIS were all multifocal, whereas all infiltrative tumours were unifocal with a mean size of 13 mm (SD 5.6mm) at their greatest dimension. Breast-conservative treatment and radical surgery were performed in 17 and 10 cases, respectively. The mean duration of surgery was 111 (59-193) minutes.

Invasive ductal, lobular, mucinous and tubular carcinomas were found in 17, 1, 2 and 1 case, respectively. One tumour showed lymphovascular invasion. Out of the 21 infiltrative breast carcinoma, ER, PR and c-erbB2 overexpression was found in 13, 10 and 1 case, respectively.

Lymphoscintigraphy. In 3 cases (3/27), the lymphoscintigraphy did not show any SLN. In 24 cases, the lymphoscintigraphy was conclusive, showing at least one SLN. In total, 51 SLNs out of 77 were visualized preoperatively by lymphoscintigraphy (efficiency: 66%).

Preoperative detection of axillary drainage with the CarolIReS camera. In all cases, axillary drainage was identified with the CarolIReS camera, especially in 11% of procedures in which no drainage was shown by conventional lymphoscintigraphy. In order to quantify axillary drainage, a signal-to-background ratio can be derived as a simplified figure of merit (FOM) to define a lower limit. The signal and the background are represented by the maximum value and the mean value obtained inside the projection. The average preoperative projection FOM was 7.3 (2.8-24.2) whereas for the postoperative projection, the FOM significantly decreased to a value of 4.2 (2.5-7.3). Figure 1A and B show the acquired projection obtained from conventional lymphoscintigraphy and Figure 1C shows the projection obtained from the CarolIReS camera for one of the procedures in which no axillary drainage was observed by lymphoscintigraphy.

Axillary surgery with the gamma probe. Using the CarolIReS probe, a total of 76 SLNs were removed, corresponding to a mean number of 2.9 (0-8) SLNs per breast.

Postoperative assessment using the CarolIReS camera. In 24 cases, postoperative assessment showed no residual SLN. Figure 1C shows a preoperative image of an SLN obtained by means of the CarolIReS camera and Figure 1D is the postoperative assessment showing no residual SLN.

In the third case (Table II), conventional lymphoscintigraphy showed only one SLN, which was also detected by the CarolIReS camera then removed and measured (9.6 kBq). It was then analysed by frozen sections, which revealed no cancer cells. During this analysis, the exploration of the axillary area with the CarolIReS camera allowed the identification of a second SLN with low activity of 0.5 kBq. Data concerning this case have been reported (20). The histological examination revealed a macrometastasis occupying the whole structure of this SLN without residual sinusoidal macrophages. Axillary clearance was then performed, followed by a postoperative image which proved that no SLN remained.

Pathological lymph node characteristics. All SLNs were submitted to an extemporaneous analysis (with frozen sections). Among these 77 SLNs, 5 were found to be invaded by cancer cells, removed from 4 different patients. On these patients, complete axillary clearances were performed during the same surgical operation. Serial section and cytokeratin immunodetection showed cancer cells in 8 other SLNs removed from four other patients. In total, there were 13 metastatic SLNs (2 micrometastases and 11 macrometastases). Four complete axillary clearances were performed during a second operation. Data relating to the 8 patients with positive SLN are summarized in Table II.

Activity of SLN and comparison with pathological lymph node characteristics. In a previously published paper (17), we demonstrated that SLN activity and size are not correlated. Figure 2A shows the measured activity of the 77 SLNs (64 negative SLNs, 11 macrometastases and 2 micrometastases). The mean SLN activity was 9.40 kBq (0.06-59.20) with a most probable value of 1.1 kBq, representing 0.5‰ of the injected activity. For the 13 metastatic SLNs, Figure 2B shows that SLN activity and size are not correlated.

Follow-up. No mammary or axillary recurrence and no metastases were diagnosed during the one year follow-up.

Discussion

Our study aimed to evaluate the performance of the CarolIReS camera in checking preoperative axillary drainage and postoperative removal of SLNs. The study included a series of 25 patients with breast cancer justifying SLN biopsy. We demonstrated the usefulness of the CarolIReS camera in the detection of axillary drainage and residual SLNs with low activity (less than 1 kBq). Our findings suggest that the use of the intraoperative gamma camera at the end of the surgery could reduce the false-negative rate of the SLN procedure.

In order to be effective, intraoperative gamma cameras must have three qualities. Firstly, their detection efficiency must be adequate. In our study, the detection efficiency of the CarolIReS

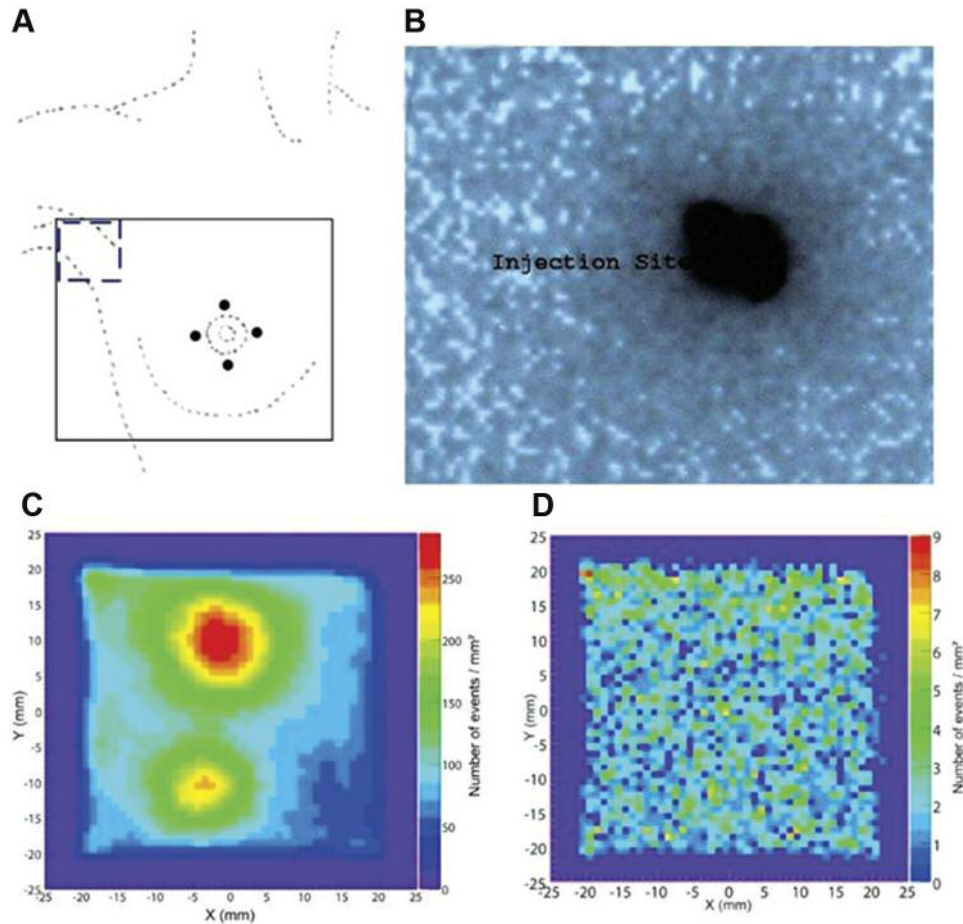


Figure 1. A) Schematic representation of the right breast. The four black circles indicate the subareolar radioisotope injection points. The position of the black rectangle represents the lymphoscintigraphy area. B) The lymphoscintigraphy shows the subareolar injection site with no axillary drainage. C) The 50×50 mm² CarolIReS camera image shows two SLNs where the image position is indicated by the blue dashed square in Figure 1A. D) The postoperative image obtained with the CarolIReS camera shows the absence of residual SLNs.

camera was 2.2 cps/kBq for ^{99m}Tc activity in an SLN at the time of the surgery. Considering radioprotection criteria, the recommended injection dose should be low, approximately 18 MBq (21). In published series, when radiocolloids are injected the day before surgery, average SLN activity ranges from 0.1 to 1% of the injected activity (22, 23). This mean value of SLN activity is significantly higher than our measured mean value of 0.5%. Moreover, when SLNs are massively invaded by cancer cells, they contain a limited number of macrophages, cells that retain radiocolloids (24); SLN activity can thus be very low. In our series, the activity of positive SLNs was less than 10 kBq in more than half of the cases. In a previously published paper (17), we demonstrated that SLN activity and size are not correlated. This lack of correlation is again confirmed in this study for 13 metastatic SLNs.

Secondly, the image acquisition time of intraoperative gamma cameras should be short. With the CarolIReS camera, four images are necessary to map the entire axillary area (2

minutes for each image, 8 minutes to map the entire axillary area). To reduce this acquisition time, the IPHC has developed a new camera with a FOV of 100×100 mm² allowing complete axillary mapping in 2 minutes.

The third requirement of the camera is that it must be manoeuvrable. For ease of use, our camera is placed on an articulated arm. Based on our experience, the CarolIReS camera appears to meet the afore mentioned quality requirements. A new clinical trial is scheduled for 2008 to compare the performance of the CarolIReS camera (FOV 100×100 mm²) with that of lymphoscintigraphy.

Conclusion

The use of intraoperative gamma cameras in operating theatres is still in an early phase. Preliminary results show, however, that they can replace conventional gamma cameras. Moreover, these intraoperative cameras could be used to

Table II. Summary of the series of 8 patients with positive SLN.

Case number	Age (years)	Tumour type	Tumour size (mm)	Breast surgery	Lympho-scintigraphy (SLN number)	Axillary surgery (SLN number)	SLN Activity (kBq)	EE	Camera Control (SLN number)	SS	Immediate AC	Postpone AC
#1	58	Ductal	17	BC	3	3	50.0	pN0	0	+	No	Yes
							0.3					
							4.4					
							4.4					
#2	71	Ductal	16	BC	1	4	0.4	pN0	0	-	No	Yes
							0.2					
							2.8					
							1.6					
#3	44	Ductal	13	BC	1	1	9.6	pN0	pN1	+	Yes	No
							9.6					
#4	47	Ductal	25	M	0	3	58.0	pN1	0	+	Yes	No
							18.0					
#5	43	Ductal	23	BC	3	3	60.0	pN1	0	+	Yes	No
							0.2					
		Ductal	8	BC	3	3	5.4	pN0	0	-	No	No
							0.5					
#6		Ductal	11	BC	1	1	7.4	pN0	0	+	No	Yes
							0.9					
#7	51	Ductal	11	M	4	7	4.1	pN1	0	+	Yes	No
							3.0					
		Tubular	8	M	3	3	18.0	pN0	0	-	No	No
							0.3					
#8	32	Ductal	12	BC	2	1	3.0	pN0	0	+	No	Yes
							0.06					
							0.06					
							0.06					

EE: Extemporaneous examination; SS: serial section; +: positive SLN, -: negative SLN; AC: axillary clearance; BC: breast conservation; M: mastectomy.

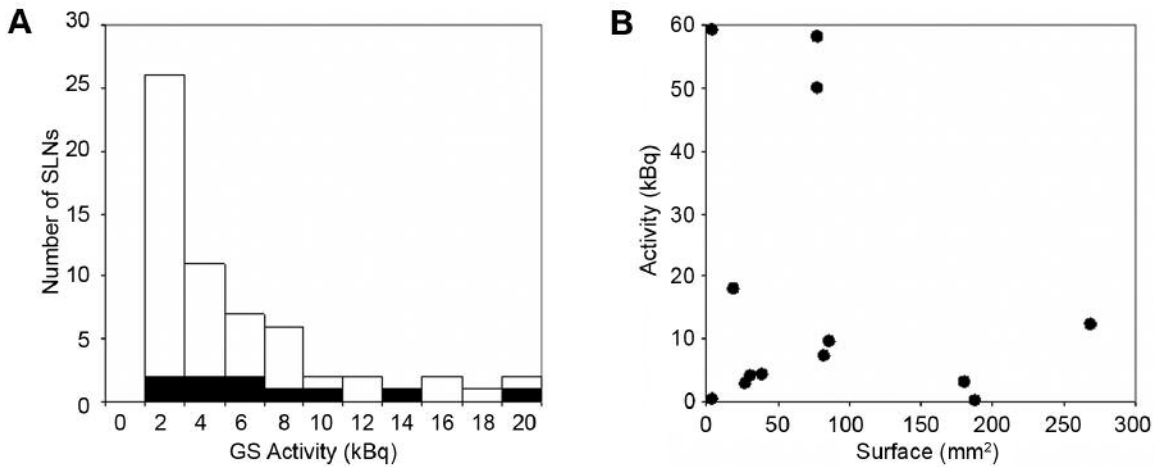


Figure 2. A) Activity of 77 SLNs (64 negative SLNs in open blocks, 11 macrometastases and 2 micrometastases in closed blocks). B) Plot of the activity versus the size of 13 metastatic SLNs

visualize extra-axillary SLNs (intramammary or internal) and also to assess the resection of nonpalpable breast lesions. Finally, young surgeons may also find these intraoperative cameras helpful to accelerate their learning curve.

Acknowledgements

We wish to thank Dr MC Rio and Pr D Huss for their helpful contribution, and Drs Jean-Louis Mehl, Roland Schaeffer and Doris Frankhauser who carried out the anaesthesias. We are grateful for the high-quality contribution of the ImaBio project engineers and technicians.

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Received May 9, 2008

Revised June 2, 2008

Accepted June 4, 2008