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Title: Sentinel node detection in early breast cancer with intraoperative portable gamma camera: UK experience

Article Type: Original Research Article Section/Category: Surgery and Gynecology
Keywords: portable gamma camera; intraoperative lymphoscintigraphy; sentinel node biopsy

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Purpose: Access to nuclear medicine department for sentinel node imaging remains an issue in number of hospitals in the UK and many parts of the world. Sentinella® is a portable imaging camera used intra-operatively to produce real time visual localisation of sentinel lymph nodes.
Methods: Sentinella® was tested in a controlled laboratory environment at our centre and we report our experience on the first use of this technology from UK. Moreover, preoperative scintigrams of the axilla were obtained in 144 patients undergoing sentinel node biopsy using conventional gamma camera. Sentinella® scans were done intra-operatively to correlate with the pre-operative scintigram and to determine presence of any residual hot node after the axilla was deemed to be clear based on the silence of the hand held gamma probe.
Results: Sentinella® detected significantly more nodes compared with CGC ($p < 0.0001$). Sentinella® picked up extra nodes in 5/144 cases after the axilla was found silent using hand held gamma probe. In 2/ 144 cases, extra nodes detected by Sentinella® confirmed presence of tumour cells that led to a complete axillary clearance.
Conclusions: Sentinella® is a reliable technique for intra-operative localisation of radioactive nodes. It provides increased nodal visualisation rates compared to static scintigram imaging and proves to be an important tool for harvesting all hot sentinel nodes. This portable gamma camera can definitely replace the use of conventional lymphoscintigrams saving time and money both for patients and the health system.

***Title Page**

Sentinel node detection in early breast cancer with intraoperative portable gamma camera: UK experience

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***Highlights (for review)**

Highlights

- Sentinella® is a reliable tool for intraoperative localisation of radioactive nodes
- Sentinella® detected significantly more nodes than the conventional gamma camera
- This portable gamma camera can replace the use of conventional lymphoscintigrams

Abstract

Purpose: Access to nuclear medicine department for sentinel node imaging remains an issue in number of hospitals in the UK and many parts of the world. Sentinella® is a portable imaging camera used intra- operatively to produce real time visual localisation of sentinel lymph nodes.

Methods: Sentinella® was tested in a controlled laboratory environment at our centre and we report our experience on the first use of this technology from UK. Moreover, preoperative scintigrams of the axilla were obtained in 144 patients undergoing sentinel node biopsy using conventional gamma camera. Sentinella® scans were done intra-operatively to correlate with the pre-operative scintigram and to determine presence of any residual hot node after the axilla was deemed to be clear based on the silence of the hand held gamma probe.

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Conclusions: Sentinella® is a reliable technique for intra-operative localisation of radioactive nodes. It provides increased nodal visualisation rates compared to static scintigram imaging and proves to be an important tool for harvesting all hot sentinel nodes. This portable gamma camera can definitely replace the use of conventional lymphoscintigrams saving time and money both for patients and the health system.

Keywords: portable gamma camera; intraoperative lymphoscintigraphy; sentinel node biopsy

Introduction

Sentinel Lymph Node biopsy (SLNB) is a standard practice for staging the axilla in breast cancer. The major advantage of staging with SLNB compared to axillary lymph node dissection (ALND) is the significantly reduced patient morbidity such as lymphedema, seroma, impaired shoulder morbidity, loss of sensation etc [1]. Moreover, assessment of the sentinel lymph node at the time of surgery makes axillary clearance feasible during the same procedure, omitting the need for a second operation and decreasing the associated health system costs as well as patients' distress [2].

Radiocolloid injection is generally performed in the nuclear medicine department within 24 h prior to surgery according to institutional policies [3]. Following injection, lymphoscintigraphy is the first step in the lymphatic mapping procedure, and the images are considered a “road map” guiding the surgeon. Lymphoscintigraphy aims to identify the number and location of sentinel nodes which are potential sites of metastatic disease, to demonstrate sentinel nodes with aberrant drainage (i.e. nodes outside normal lymphatic drainage basins), as well as to try to distinguish SLNs from second-tier lymph nodes.

Although planar lymphoscintigraphic imaging is an important element in lymphatic mapping and identifies SLNs in more than 95% of breast cancer patients [4], issues regarding increased costs and access to nuclear medicine department in number of hospitals in the UK and rest of the world still exist [5,6]. Moreover, scheduling surgery before significant decay of the radioactive isotope or organising wire localisation of the primary tumour for the same patient poses scheduling difficulties in the operative room [7].

Sentinella® (Oncovision, Valencia, Spain) is a recently introduced portable imaging gamma camera used intraoperatively to produce real time visual localisation of SLNs [8,9]. It includes a detector with an area of 4 x 4 cm2 and two pinhole collimators with diameters of 4 mm and 2.5 mm. When the camera is placed at a distance of 15 cm from the imaging level, the captured field is 20 x 20 cm2.The intrinsic spatial resolution of the camera is 1.8 mm [10].

In the present study, Sentinella was initially tested in a controlled laboratory environment at our centre to assess its performance and this was followed by the first use of this device in breast cancer patients in the UK. In the laboratory setting our aim was to compare the sensitivity and spatial resolution of the Sentinella® and a conventional gamma camera (CGC) used for sentinel node imaging. In the clinical setting we aimed to evaluate the feasibility of Sentinella® in identifying sentinel lymph nodes intra operatively and compare its detection rate with that of preoperative CGC.

Materials and Methods

We assessed the sensitivity and spatial resolution of the Sentinella® mobile gamma camera by comparing it with the performance of a GE multi-purpose rectangular (MPR) conventional single head gamma camera normally used for sentinel node imaging. Measurements on the MPR were made using the parallel-hole low energy high resolution collimator used for sentinel node imaging. Technetium-99 m pertechnetate was used in all measurements.

Sensitivity measurements on Sentinella® were made using a point source. Sensitivity measurements on the MPR gamma camera were made using a 10 x 10 cm2 sensitivity phantom.

Spatial resolution of MPR was measured by calculating the full width half maximum (FWHM) of a line profile measured perpendicular to the image of a capillary tube filled with high activity concentration technetium-99 m pertechnetate. For Sentinella®, spatial resolution was measured at the centre and at the edge of the field of view.

Sensitivity and spatial resolution of Sentinella® was further compared with the MPR in a simulated axilla (Fig. 1) [11]. A special simulator mimicking the axilla and seeds containing 10 kBq, 100 kBq, 500 kBq of radiocolloid 99mTc, mimicking lymph nodes were used. The different seeds were placed at several depths in the axilla, at 3 cm, 5 cm and 8 cm from the skin. For each combination of depths and radioactivities we obtained four images with Sentinella® and two with the MPR. Sentinella® was placed first 10 cm and then 1 cm away from the axilla and images were recorded at 1 min and at 2.5 min for every position. The MPR was placed 20 cm away from the axilla and one anterio-posterior and one lateral image were recorded at 2.5 min. Three independent observers reported the number of radioactive spots on each image.

Between September 2009 and May 2012, 146 patients who did not have known involved axillary lymph nodes (N0) and were scheduled for SLNB at our Breast Unit were prospectively enrolled in the current study. In 2 cases sentinel lymph nodes were not visualised in preoperative CGC and intraoperative Sentinella® scans. SLNB was performed based on the blue dye and they were excluded from the study. Other exclusion criteria included clinically or ultrasonographically positive axilla, previous breast or axillary surgery, previous loco-regional radiotherapy. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their written informed consent prior to surgery and inclusion in the study. Patients' demographics and tumors' characteristics are summarized in Table 1.

15-20MBq in 0·2ml ^{99m}Tc-nanocolloid (Nanocoll®; GE Healthcare) was injected intradermally in subareolar area in index quadrant. Planar static scintigraphy was done in anterior and lateral projections, 10 minutes per projection. The location of the SLN (shortest skin-to-node) distance was marked on the skin with indelible marker pen. Parameters recorded for each image included number and location of sentinel nodes as well as presence of higher echelon nodes. In case of no visualisation of sentinel nodes delayed images were acquired.

SLNB was performed within 18 h using the combined technique of blue dye (Patent blue 2.5%, Guebert, France) and

radioactive isotope for node localisation [12]. Intraoperative Sentinella® scans were performed in all patients and the number of identified nodes was compared with the respective number of nodes detected by conventional gamma camera (Fig. 2). The portable gamma camera was sterile draped in such a way to allow placement and movement above and within the surgical field. A first image was acquired to assess the surgical field and identify radioactive uptake. Sentinella incorporates a LED pointer which displays a red cross over the patient's skin. The centre of the cross corresponds to the centre of the image on the computer screen and makes it easier to locate radioactive nodes and plan skin incisions accordingly. Further Sentinella® scans were performed after the axilla was deemed clear by silent activity of the device's in-built hand held gamma probe.

All hot, blue and any pathologically palpable nodes were excised and sent for intraoperative analysis. In case of micro- or macro- metastases, axillary lymph node clearance was performed during the same procedure.

Statistical analysis

Data analysis for this study was generated using SAS software, Version 9.3 for Windows 7. The Wilcoxon signed rank sum test was used to compare the number of nodes detected by the two methods. The range or standard deviation was used as a measure of dispersion.

Results

The variation of sensitivity with distance from the pinhole in the centre of the field of view of the Sentinella® mobile gamma camera using both the green (2.5 mm pinhole) and blue (4 mm pinhole) collimators as well as variation of sensitivity of the GE MPR with distance from the collimator face are shown in Fig. 3. The blue collimator has a larger pinhole so it is more sensitive, although its spatial resolution is not as good. As expected, the sensitivity falls off roughly as 1/r2. By contrast, the sensitivity of the MPR is almost constant. For distances up to about 7 cm, Sentinella® with the blue collimator is more sensitive than the MPR. However, with further increase in the distance its sensitivity drops off rapidly.

Variation of relative sensitivity of Sentinella® with distance from the centre of field of view, measured in a plane parallel to the detector at a distance of 4.0 cm from the pinhole is demonstrated in Fig. 4. The sensitivity of the GE MPR gamma camera is uniform across the field of view.

According to simple theory, the sensitivity of the pinhole camera is predicted to vary as (cosq)3 where q is the angle of incidence. The measured variation in sensitivity is close to the predicted variation. Variation of spatial resolution of Sentinella® with distance from the pinhole and variation spatial resolution of the MPR with distance from the collimator surface are shown in Fig. 5. For both collimators, the spatial resolution of the Sentinella® at the centre of the field of view is slightly better than at the edge of the field of view and better than specification. For the MPR, spatial resolution does not depend on the position in the field of view. Close to the detector the spatial resolution of the Sentinella® is similar to the MPR. However, as distance from the detector increases the spatial resolution of the

Sentinella® gets worse more rapidly than the MPR. In the simulated axillary experiment, 68 Sentinella® and 34 MPR images were evaluated. Sentinella® detected high radioactivity (500 kBq) faster than MPR (1 vs 2.5 min).

In cases of low radioactivity (10 kBq), Sentinella® was equally accurate and faster than MPR, when placed close to the skin.

When we looked at intermediate radioactivity (100 kBq) Sentinella® was equally accurate and faster than MPR, regardless of its distance from the skin.

When we used two seeds with intermediate radioactivity and placed them close to each other (1 cm) Sentinella was faster and equally accurate as compared to MPR in detecting the seeds when placed close to the skin.

In cases of three seeds with low, intermediate and high radioactivity placed close to each other, Sentinella® was equally accurate in detecting the seeds, but was not faster than MPR.

In the clinical setting with 144 patients, intra-operative Sentinella® scans detected 267 SLNs with a median of 2 (range 1-6 nodes) per patient compared with 209 nodes with a median of 1 (range 1-5 nodes) per patient by CGC scans (Fig. 6); this difference was statistically significant by the Wilcoxon signed rank sum test ($S = -564.5$, $p < 0.0001$). In 85 patients the number of nodes detected was equal; in 48 patients Sentinella detected more nodes and in 10 patients CGC detected more nodes.

Sentinella® demonstrated a serial decay in activity with removal of every hot node and its LED guidance helped in detecting residual nodes. Sentinella® picked up extra nodes in 5/144 cases after the axilla was found silent using hand held gamma probe. In 2/144 cases extra nodes depicted on Sentinella® had macrometastatic presence of cancer and in one case it was the only involved lymph node which changed the surgical management as it led to a complete axillary clearance.

Discussion

The disease status of the axillary lymph nodes is the most significant prognostic factor for patients with early-stage breast cancer [12] and sentinel lymph node biopsy (SLNB) has now been established as an accurate method of staging the axilla. Sentinel node visualisation with a CGC before surgery and intraoperative detection with a hand-held gamma probe have become routine practise in most breast cancer treatment centres.

Pre-operative lymphoscintigraphy is mainly used to guide the surgeon in sentinel node harvesting, but logistical issues regarding nuclear medicine availability and scheduling as well as cost-effectiveness analyses have led to the development of portable gamma cameras allowing intraoperative localisation of SLNs [6].

Sentinella®, a portable gamma camera fitted with a pinhole collimator to obtain a field of view of 20 x 20 cm has been previously reported as useful in centres with non-availability of a conventional gamma camera preoperative image since it was able to depict sentinel nodes in 88% of the cases [13].

We tested Sentinella® in a controlled laboratory environment and found that its sensitivity at distances less than 7 cm

was higher than MPR. This illustrates one reason why it is important to get the camera as close to the patient as possible. Obviously Sentinella® can be positioned closer to the patient than the MPR. Even so, it may not be possible to achieve the same sensitivity as the MPR for deep nodes. This will affect the camera's ability to detect deep low activity nodes.

The resolution is better for the green pinhole; however, its sensitivity is not as good as that with the blue pinhole (see above). Sentinella® resolution is comparable with the MPR for objects close to the camera i.e. ~ 5 cm, but gets worse more rapidly as you move away from the camera. It is important to get the detector as close to the patient as possible whilst using Sentinella®. The flexibility of the system on a hydraulic arm makes it easy to manoeuvre the camera head and place it close to the axilla.

A study comparing preoperative lymphoscintigraphy with intraoperative visualisation of sentinel nodes performed with Sentinella® has shown an improved detection rate of SLNs in cutaneous malignancies (10). In a recent breast cancer study, authors did not identify any additional sentinel node by Sentinella® that was not detected by conventional gamma camera [13]. On the other hand, in a study evaluating the performance of an intraoperative gamma camera named CarolIReS in 25 breast cancer patients, a case of residual highly metastatic SLN was identified and excised [14].

Overall, intra-operative Sentinella® scans were significantly better at detecting nodes than CGC scans ($p < 0.0001$). In one-third of the patients (48/144) Sentinella detected more nodes. More important, however, is that in 2/144 cases extra nodes depicted on Sentinella were found positive with macrometastases. Furthermore, in 1 case, the extra node identified only by Sentinella® was the only positive node and changed patient's management, as it led to a complete axillary clearance. Therefore, we demonstrate not only the reliability and effectiveness of Sentinella in identifying sentinel lymph nodes but also the increased pickup of hot nodes which can cause further axillary surgery and possible upstaging.

The measurement of post-excision radioactivity can lead to the detection of additional SLNs in the head and neck region [15]. Similarly, in our breast cancer patients, after sentinel node retrieval, further Sentinella® images were acquired to check for any residual sentinel/second-tier nodes. Indeed, Sentinella® picked up extra nodes in 5/144 cases after the axilla was found silent using hand held gamma probe.

A number of pitfalls and errors in sentinel node interpretation have been previously discussed [16]. Indeed, the nearest node is not always on a direct drainage pathway from the tumour or the one with the highest count rate and the first node that is visualised may not be the only SLN. Some of the radiocolloid may pass through the first node and lodge in a subsequent node. Such nodes are on a direct drainage pathway from the tumour and should be considered to be SLNs. They are clinically as important as SLNs in recognized lymph node basins and false negative rates have been shown to decrease by increasing the number of resected nodes [17]. Thus, all hot and blue nodes must

be harvested [18].

Timing of imaging is another important issue that influences node visualisation. Whilst the majority of SLNs may be visible soon after injection of the radiocolloid (within 15-20 min), a small proportion require later imaging [19]. The majority of SLNs should be visible by 2.5 h of radiocolloid injection [20], but it is not convenient for the patients to stay for so long in nuclear medicine departments, especially since which patient will require later imaging to allow all lymphatic tracks to be visualised is not known at the time of pre-operative CGC imaging. This may account for the increased number of hot nodes identified by Sentinella®.

Conclusion

This study confirms the excellent sensitivity and specificity of Sentinella® in localisation of radioactive nodes. Our results demonstrate a clear advantage of using Sentinella® over CGC for SLN detection in early breast cancer in terms of increased SLN detection and minimized cost and scheduling requirements. Thus, this portable gamma camera can replace the use of conventional lymphoscintigrams saving time and cost both in patients and health care providers.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their written informed consent prior to surgery and inclusion in the study.

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Figure Legends

Fig. 1 Sentinella® used in a lab environment on a sentinel node simulator

Fig. 2 Sentinel node image with conventional gamma camera and Sentinella®

Fig. 3 Variation of sensitivity with distance for Sentinella® and GE MPR gamma cameras

Fig. 4 Variation of sensitivity of Sentinella® with distance from the centre of the field of view

Fig. 5 Variation of spatial resolution with distance for Sentinella® and MPR gamma cameras

Fig. 6 Frequency distribution showing number of lymph nodes detected by conventional gamma camera and Sentinella®

Table 1

Table 1. Patients' and Tumours' Characteristics

Parameter	
Age (mean ± SD)	62.2 ± 12.36
Histological Type (n=144)	
Invasive	
Invasive Ductal Carcinoma	102 (70.8%)
Invasive Lobular Carcinoma	20 (13.9%)
Other	11 (7.6%)
Non-invasive	
Ductal Carcinoma In Situ	10 (6.9%)
Lobular Carcinoma In Situ	1 (7%)
T – status (n=144)	
T1a	6 (4.2%)
T1b	14 (9.7%)
T1c	49 (34%)
T2	59 (41%)
T3	16 (11.1%)
Tumor Grade (n=133)	
I	25 (18.8%)
II	67 (50.4%)
III	41 (30.8%)
Lymphovascular invasion (n=133)	
Yes	34 (25.6%)
No	99 (74.4%)
ER positivity (n=133)	
Yes	102 (76.7%)
No	31 (23.3%)
PR positivity (n=133)	
Yes	88 (66.2%)
No	45 (33.8%)
HER2 positivity (n=133)	
Yes	43 (32.3%)
No	90 (67.7%)
Type of operation (n=144)	
Mastectomy	48 (33.3%)
Quadrantectomy	3 (2.1%)
Wide local excision	83 (57.6%)
Sentinel node biopsy	10 (6.9%)

Figure 1

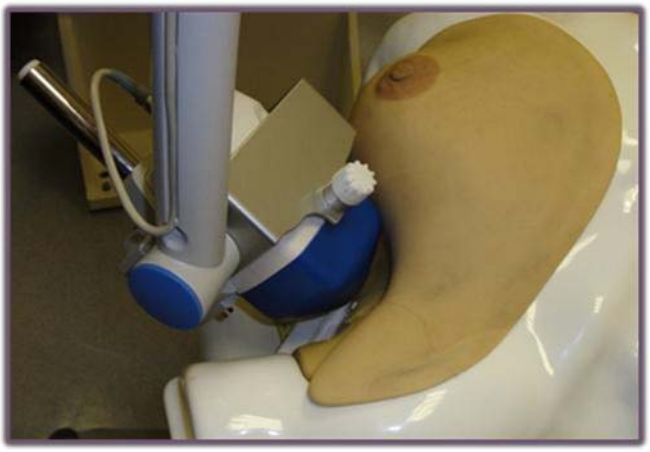
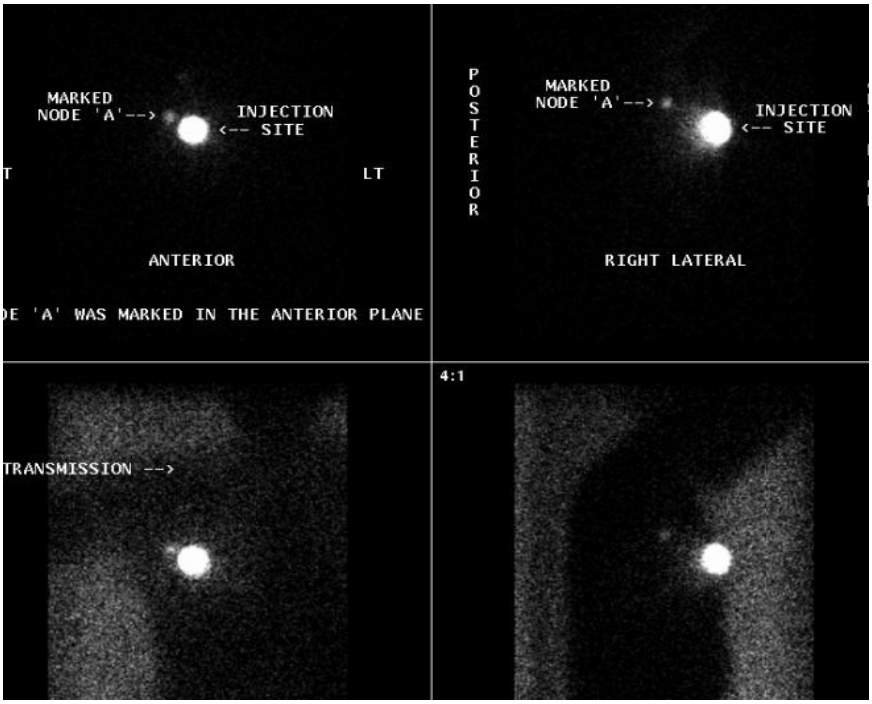


Figure 2


MARKED
NODE 'A'-->
INJECTION
<-- SITE
T
LT
ANTERIOR
E 'A' WAS MARKED IN THE ANTERIOR PLANE
POSTERIOR
MARKED
NODE 'A'-->
INJECTION
<-- SITE
RIGHT LATERAL
TRANSMISSION -->
4:1

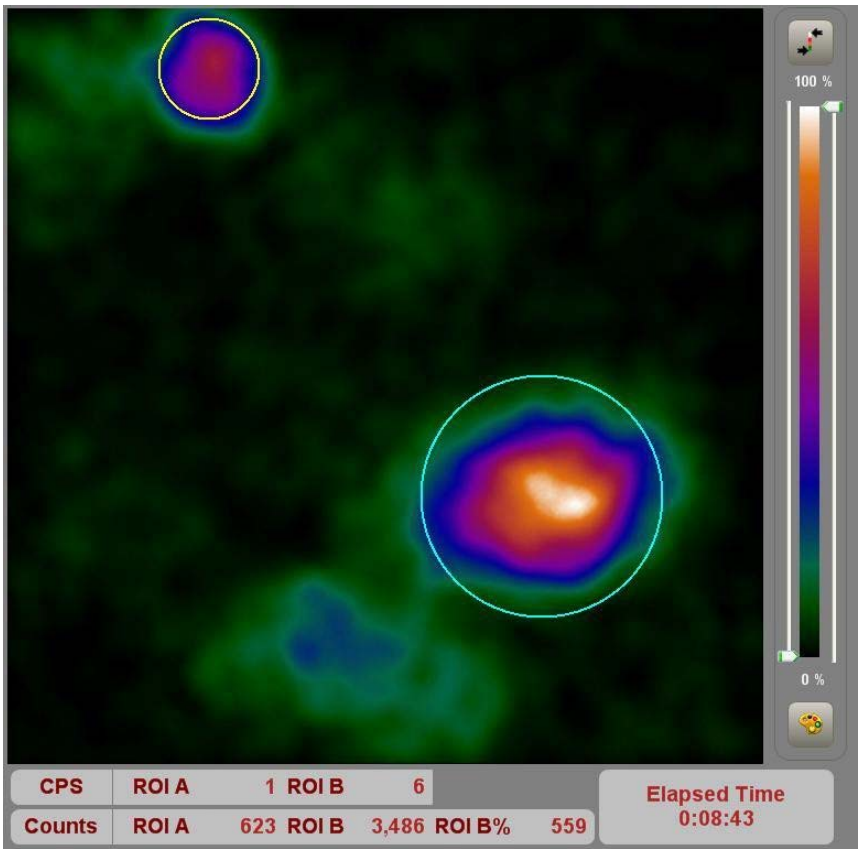

100 %
0 %
CPS
ROI A 1 ROI B 6
Counts
ROI A 623 ROI B 3,486 ROI B% 559
Elapsed Time
0:08:43

Figure 3

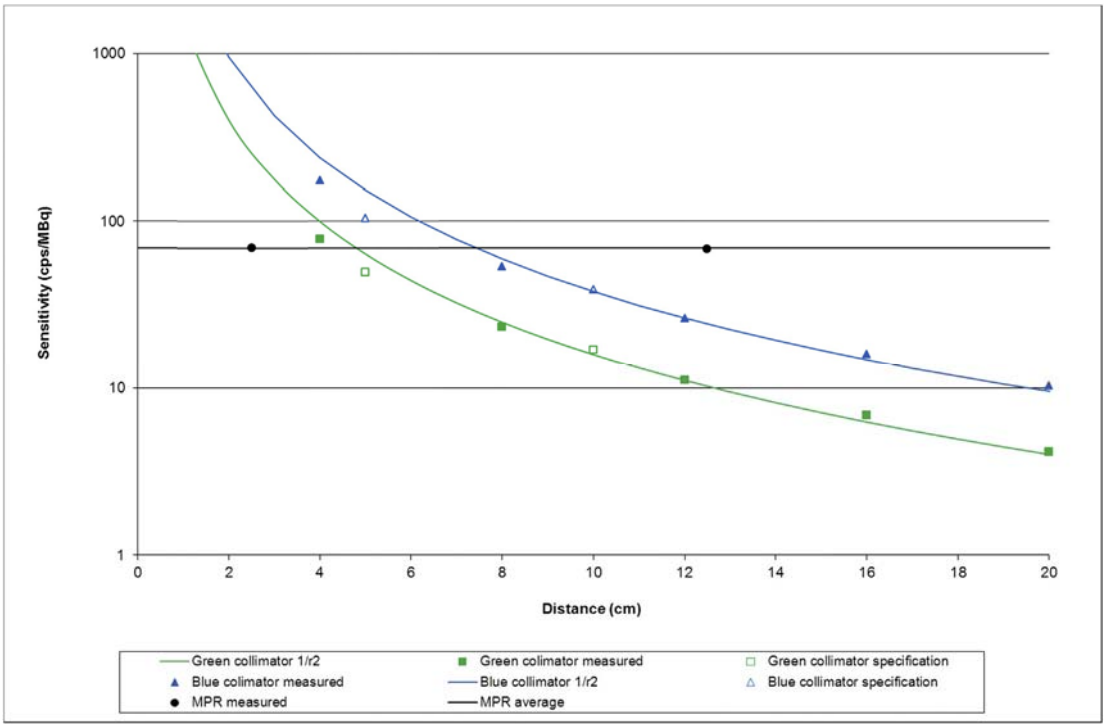

Sensitivity (cps/MBq)
1000
100
10
1
0
2
4
6
8
10
12
14
16
18
20
Distance (cm)
Green collimator 1/r2
Green colimator measured
Green collimator specification
Blue colimator measured
Blue collimator 1/r2
Blue collimator specification
MPR measured
MPR average

Figure 4

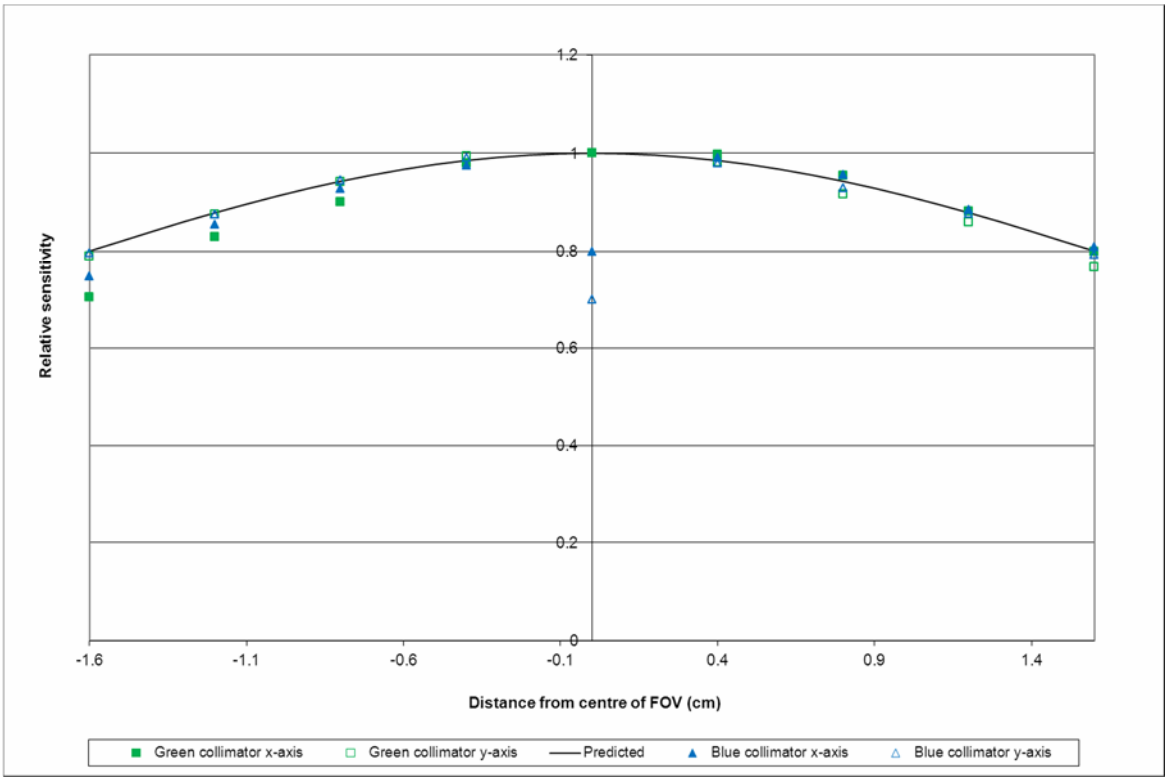

Relative sensitivity
1.2
1
0.8
0.6
0.4
0.2
0
-1.6
-1.1
-0.6
-0.1
0.4
0.9
1.4
Distance from centre of FOV (cm)
Green collimator x-axis
Green collimator y-axis
Predicted
Blue collimator x-axis
Blue collimator y-axis

Figure 5

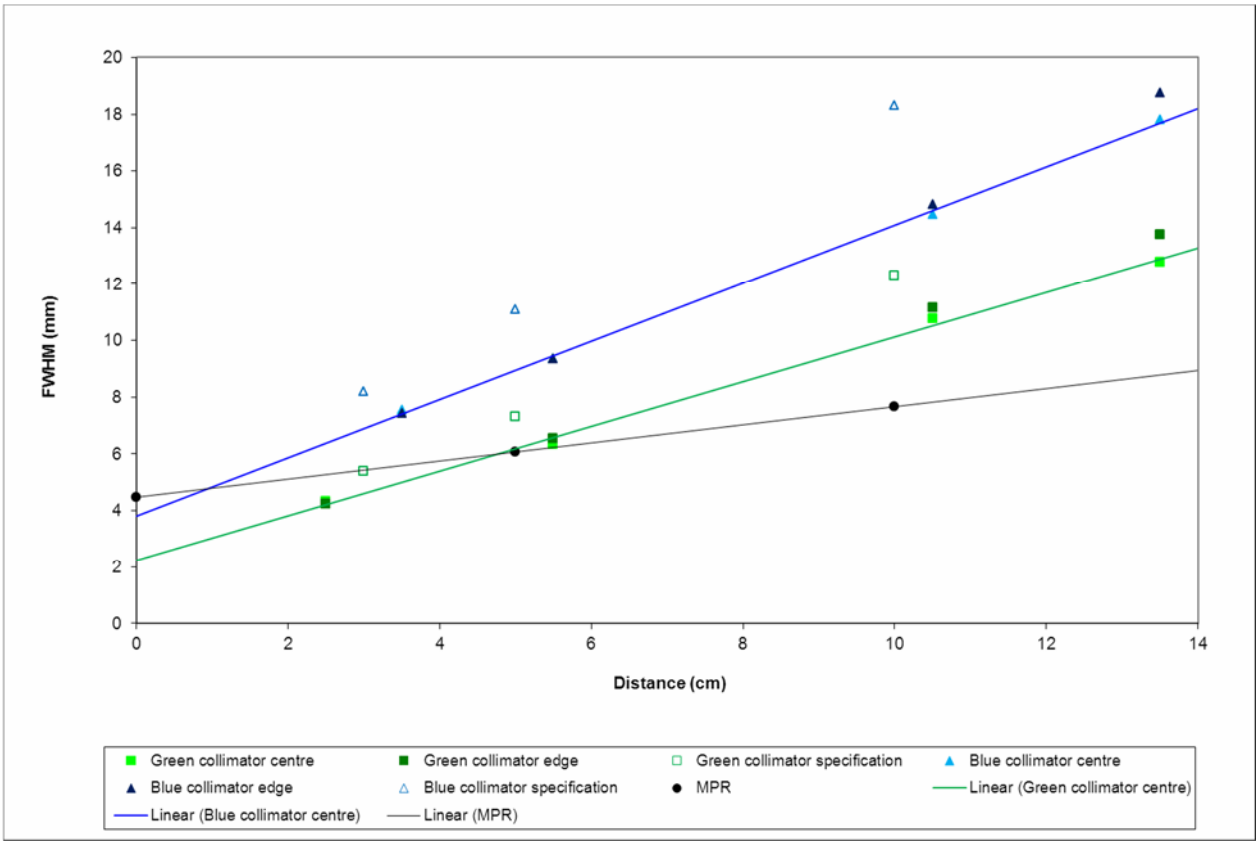
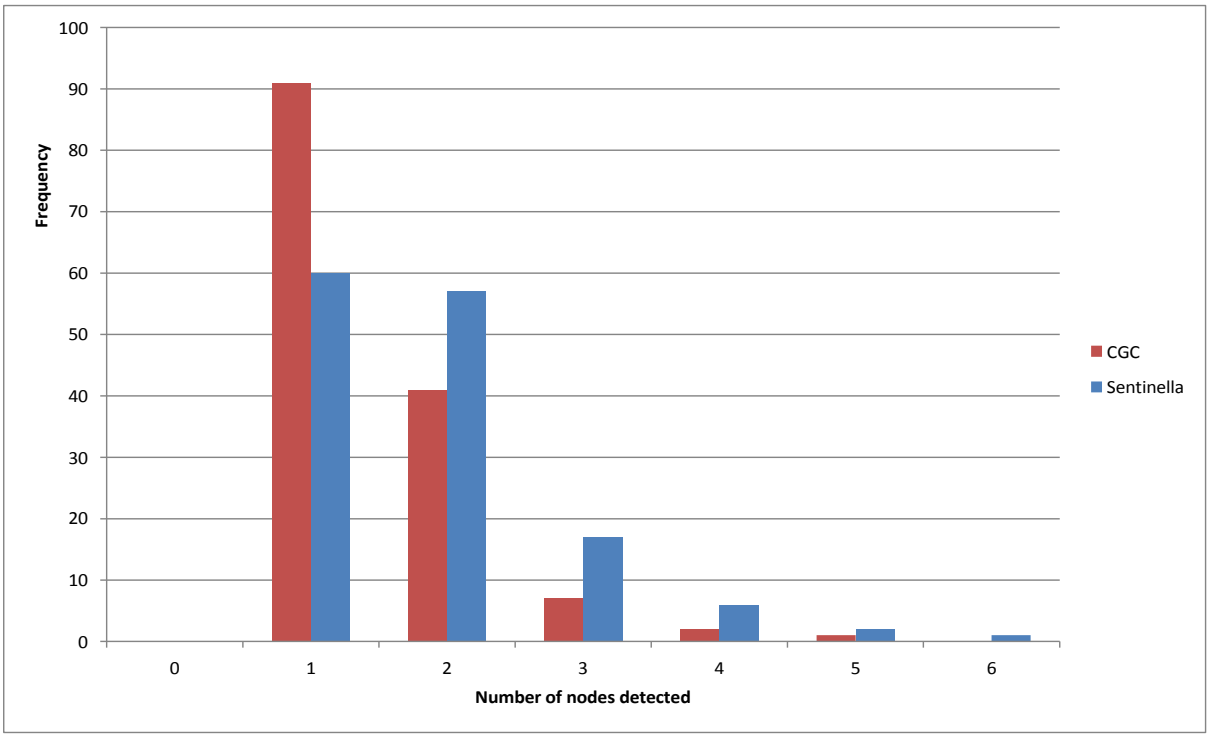

FWHM (mm)
Distance (cm)
0
2
4
6
8
10
12
14
16
18
20
Green collimator centre
Green collimator edge
Green collimator specification
Blue collimator centre
Blue collimator edge
Blue collimator specification
MPR
Linear (Green collimator centre)
Linear (Blue collimator centre)
Linear (MPR)

Figure 6


100
90
80
70
60
50
40
30
20
10
0
Frequency
0
1
2
3
4
5
6
Number of nodes detected
CGC
Sentinella