Characterization of simultaneous use of ^{125}I and ^{99m}Tc in non-palpable breast cancer surgeries

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Abstract: A new technique is being introduced to improve non-palpable breast cancer surgeries. The purpose of this method is to localize the tumour and the sentinel node using two radioactive tracers (RT): ^{125}I(Seed) and ^{99m}Tc. The present research aims to characterize the detections of these two RTs using intraoperative gamma probe to determine if the detections are independent. We validated our proposal by performing experimental tests using the RT separately and simultaneously in order to visually compare them. The results demonstrated that the interference between ^{125}I and ^{99m}Tc detections is nearly irrelevant during the surgery procedure.

I. INTRODUCTION

Breast cancer is the most common cancer in women worldwide and the second one occurred in both men and women. In 2018, more than two million of new cases appeared causing over 600.000 deaths in over the world, for both sex and all ages [1]. One of the most important factors in order to reduce its mortality, is practising an extremely accurate surgery. This issue is especially challenging when treating patients with non-palpable breast lesions, since the tumour is impossible to localize externally. Due to the need to improve localization, much less invasive and harmful techniques have been developed during the last decades:
1) Wire localization was the first one introduced. To localize the tumour a wire is inserted in the center. The most important disadvantage of this technique is the dislocation of the wire and therefore, the excision of healthy tissue.
2) Radioguided Occult Lesion Localization technique (ROLL) was implemented to overcome the limitations of the wire localization. In this case, the localization is reached using Technetium-99m (^{99m}Tc). This radioactive tracer (RT) is injected inside the breast lesion and allows its localization using intraoperative gamma probes. Gamma probes are used to detect the ionizing radiation from RT and guide the surgeons toward the area of interest. Furthermore, visualizing the lymphatic drainage of the RT helps the surgeons to identify the Sentinel Node (SN). SN is the lymph node that directly receives the drainage of the tumour cells. So that, the examination of SN evinces whether there is metastasis in breast cancer patients. The main disadvantage of ROLL is the diffusion of ^{99m}Tc resulting in an incorrect margin resection [2].
3) ROLL using Iodine-125 seed (^{125}I), ROLLIS (Radioguided Occult Lesion Localization with radioactive ^{125}I Seed) technique, consists in an encapsulated source (length:4mm, diameter:0,8mm) which avoids tissue migration and has a limited area of activity. The seed is implanted preoperatively inside the tumour and is detected using gamma probes. It allows surgeons to perform a more precise resection with less volume of healthy tissue removed.
Nowadays in Spain, surgeries of non-palpable breast cancer are being performed using simultaneous use of two different RTs: ^{99m}Tc to locate the SN and ^{125}I(Seed) guiding to the tumour.
The use of gamma probes under this situation has been demonstrated to be highly effective[3], but the head doctor of Nuclear Medicine Department of Hospital Clinic suggest that the technique has not been tested neither published in Spain. Due to the lack of validation of the method, the main objective of this work is to characterize the intraoperative gamma probes under the detection of the tumour and SN when using ^{99m}Tc and ^{125}I(Seed). On one hand, the research aims to characterize the main features of the intraoperative gamma probes detecting these two RTs, in order to provide the technical properties of the probes. On the other hand, the purpose is to verify if the detections of the two RTs are independent or might have a mutual contribution, to ensure that the tumour excision is based only on the ^{125}I(Seed) activity. So that, it must be considered during the surgical procedure by the nuclear medicine physician.

II. METHODS AND MATERIAL

A. Clinical observation

The first step of the experimental part was to perform complete follow-up of a breast cancer patient at Hospital Clinic of Barcelona:
1)The nuclear medicine physician implanted the seed inside the tumour using medical ultrasound, 24 hours before the surgical procedure. After, the ^{99m}Tc was injected into the tumour in order to drain through the lymphatic system. Finally, to ensure the correct localization of the ^{125}I(Seed), a mammography (imaging technique which uses low-energy X rays to examine the human breast for diagnosis and screening) was performed.
2)Three hours later, an SPECT (Single Photon Emission

Computed Tomography) image was obtained to visualize both the correct position of the seed and the activity of ^{99m}Tc and ^{125}I. Moreover, a lymphography (nuclear imaging to visualize the drainage of RT through lymphatic system) was performed to visualize the drainage of ^{99m}Tc through the nodes, in order to identify the SN. Finally, the RTs were detected using the portable gamma camera to check the localization of ^{99m}Tc and ^{125}I using the same equipment than in the operating room.
3)The surgical procedure was performed the next day: firstly, the nuclear medicine physician searched the tumour detecting the radiation emitted from ^{125}I using the intraoperative gamma probe. Once the tumour was found, the gynaecological surgeon removed the lesion and proceeded to analyse it. The same procedure was performed to localize the SN detecting ^{99m}Tc. Once the surgical procedure was finished, the carcinogenic tumours were removed. The analysis of SN allows to know whether there is metastasis so the patient can start the corresponding therapy.

B. Experimental set-up

The characterized intraoperative gamma probes, consist in an unit control connected to the hand-held. The probe detects the emitted radiation from RT, shows the count rate and produces a proportional sound. We decided to use the Navigator GPS TM Standard Lymphatic Mapping model, which allows us to choose in which energy window perform the detections, both ^{125}I-channel and ^{99m}Tc-channel [4]. Two kind of probes were characterized: one connected by cable which is shown in Fig(1) and a wireless probe.

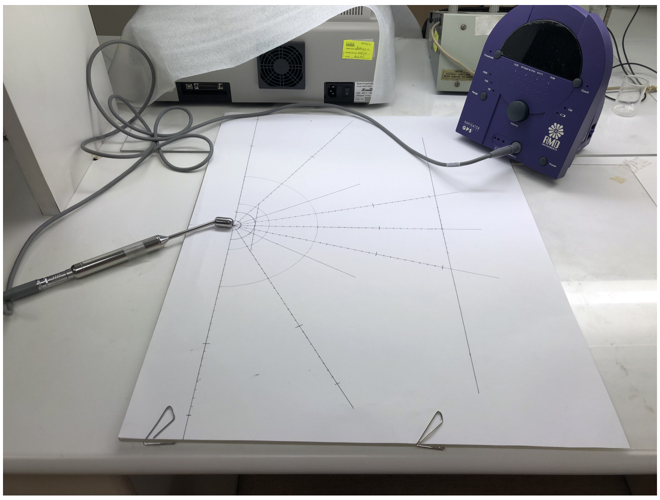

FIG. 1: Required equipment to perform the experimental tests; the designed stencil and the intraoperative gamma probe.

To characterize the intraoperative gamma probes for the detection of the two RT simultaneously, first we characterised each RT separately. According to clinical routine, different activities for both RTs were used and are described in Table(I).

	Radionuclide	Activity (kBq)
Seed 1	^{125}I	6142
Seed 2	^{125}I	3219
Seed 3	^{125}I	2738
Tc25	^{99m}Tc	925
Tc20	^{99m}Tc	740
Tc15	^{99m}Tc	550
Tc10	^{99m}Tc	370

TABLE I: Features of radionuclides used for the gamma probes characterization.

Having understood the whole process and decided the required material, some experimental tests were designed following the Quality Controls of the instrumentation of Nuclear Medicine [5]. Considering that the possible interference between the RTs might be from the ^{99m}Tc while detecting ^{125}I from the tumour, the tests were focused to quantify the interference from ^{99m}Tc to ^{125}I detection. The peak energy of ^{99m}Tc is in 140 keV, meanwhile the ^{125}I one is in 30 keV. Therefore, the scattered radiation due to Compton effect from ^{99m}Tc might interfere with the detection of ^{125}I. In order to perform the experimental tests, a stencil was designed considering all the measurements described in the quality controls which is shown in Fig(1) [6].
Finally, the experimental set-up consisted in the intraoperative gamma probe which was attached in a fixed position during all the tests, as it shows Fig(1). The probe shows in the screen the number of counts detected proportionally to the radiation detected. During the tests, RTs where placed in the designed stencil and were moved spatially and angularly: ^{125}I as an encapsulated source and ^{99m}Tc as liquid sample placed in a small plastic bubble. The experimental procedure consisted in collecting the number of counts from different RTs' position.The experiments were conducted to characterize the gamma probes analysing its properties:

- Sensitivity: is the count rate per unit of the activity produced by the radionuclide and quantifies the smallest variation that can be appreciated by the probe. To characterize the sensitivity, we measured the number of counts detected by the probe moving the radionuclide every 1 cm from 0 to 15 cm, being aligned with the probe.
- Angular and spatial resolution: quantifies the minimum angular and spatial distance between two distant objects that the probe can discern. We measured the maximum number of counts that occurred when the probe and the radionuclide were

aligned. Then the half of maximum counts was used to calculate the Full Width at Half Maximum (FWHM). The procedure was performed at 3cm and 30cm as it is defined in [5].

- Directionality: because ^{125}I is an encapsulated source, it was necessary to analyse the variation of the count rate, according to the relative angle between the probe and the ^{125}I(Seed). The directionality of ^{99m}Tc has no sense since it is liquid. We measured the number of counts by rotating the seed every 15°. The procedure was performed from 0° to 180°.

III. RESULTS

The experimental tests were performed using both probes, the wireless one and the wired. Unfortunately, using the wireless probe, a malfunction of the probe was evidenced. The Nuclear Medicine Department was notified and the probe was removed from the surgical practise and sent it for repair.
Accordingly, the experimental tests were performed using only the wired-probe.

A. Using ^{99m}Tc and ^{125}I separately

- **Sensitivity:**
The results from the measures from the three seeds detected in the ^{125}I- channel can be seen in Fig(2). The same results for three different activities of ^{99m}Tc using both ^{125}I-channel and ^{99m}Tc-channel are shown in Fig(4) and Fig(3), respectively. In all cases we observe the dependence between sensitivity and distance, from RT to the probe, as $Sensitivity \propto \frac{1}{D^2}$. The main observable difference between measurements is the sensitivity scale: in one hand, when detecting ^{99m}Tc using ^{99m}Tc-channel the sensitivity of the probe is maximum since the ^{99m}Tc peak is 140keV compared to the 30keV of the ^{125}I peak. The difference between the maximum sensitivities detecting ^{99m}Tc or ^{125}I, is about 20 no.counts/kBq. On the other hand, when detecting ^{99m}Tc in the ^{125}I-channel, sensitivity is the lowest. In this case just the scattered from ^{99m}Tc in ^{125}I window was detected, so the maximum sensitivity decreases until a factor of 10. Furthermore, we can appreciate, in the area of small distances, the effects of dead time on senstivity.
- **Spatial and angular resolution:**
Experimental tests were performed using the different seeds measured in the ^{125}I-channel, and two different activities of ^{99m}Tc measured both in the ^{125}I-channel and ^{99m}Tc-channel. FWHM was calculated and defines the spatial and the angular resolution. Analysing the results, shown in Table(II), we can verify that the resolution is independent from different activities, so resolution is an intrinsic feature of the probe. The slight variations could be as consequence of experimental errors.

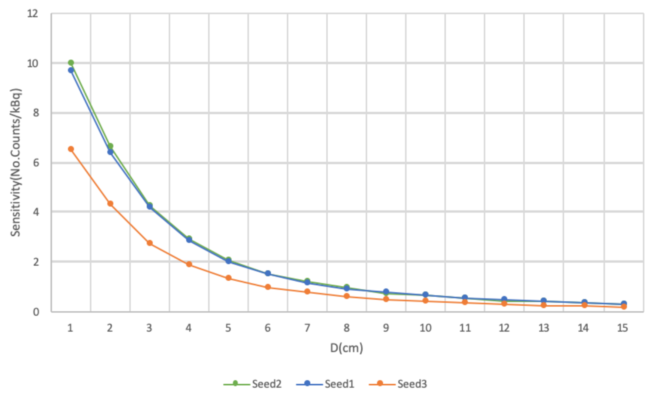

FIG. 2: Relation between the sensitivity and distance when the seeds and the probe are aligned. Measurements have been performed in the ^{125}I-channel.

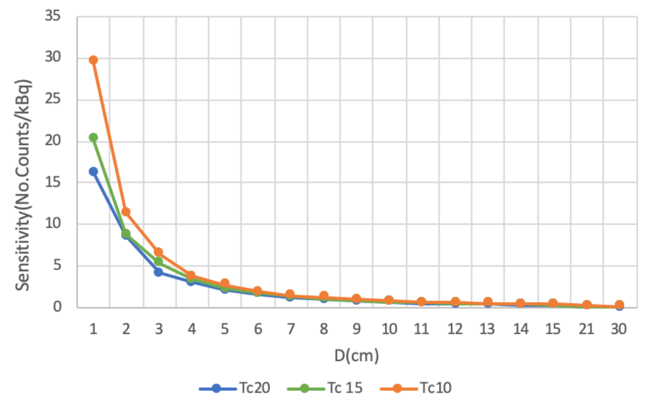

FIG. 3: Relation between sensitivity and distance when the different activities of ^{99m}Tc and the probe are aligned. Measurements have been performed in the ^{99m}Tc-channel.

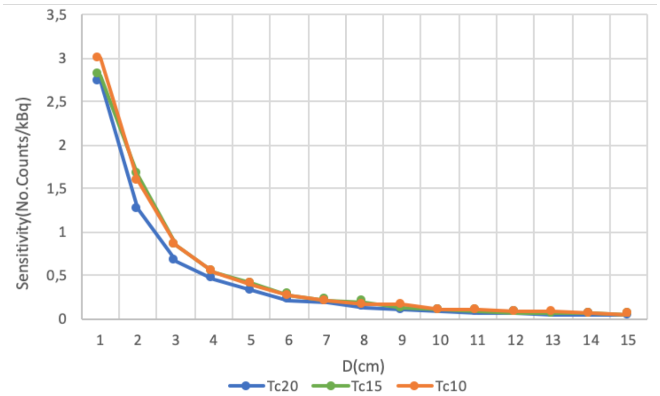

FIG. 4: Relation between the sensitivity and distance when different activities of ^{99m}Tc and the probe are aligned. Measurements have been performed in the ^{125}I-channel.

RT-Channel	SR at D=3cm	SR at D=30cm	AR at D=3cm	AR at D=3cm
Seed1-I 1	2,53	18,19	52,49	42,06
Seed2-I	2,65	20,42	52,14	41,41
Seed3-I	2,74	19,49	52,58	42,32
Tc10-Tc	3,10	18,31	60,97	51,39
Tc10-I	2,83	23,72	60,17	56,07
Tc25-Tc	3,13	24,58	63,42	50,86
Tc25-I	3,06	26,11	62,54	48,90

TABLE II: Spatial (SR) and angular (AR) resolution, in cm and ° respectively, for the tested seeds using ^{125}I-channel and for different activities of ^{99m}Tc using both ^{125}I-channel and ^{99m}Tc channel, at 3cm and 30cm. Referee to Table(I) for the names of RTs.

- **Directionality:**
  Directionality test (Fig(5)) presents unexpected results: the number of counts has a peak when the probe and the ^{125}I(Seed) are arranged with a relative angle of 90°. The only difference between the results from the different seeds is the number of detected counts which increases with higher activities.

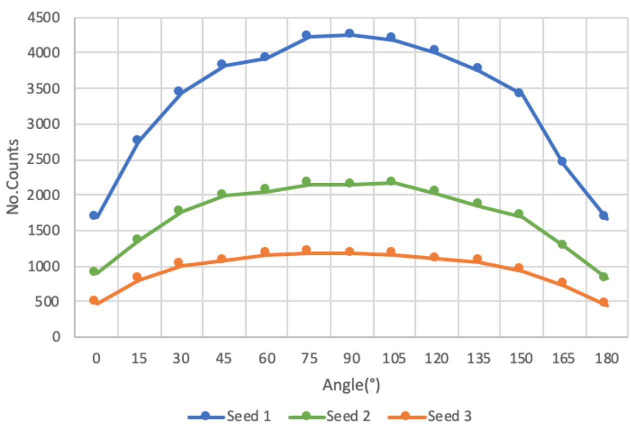

FIG. 5: Relation between the detected number of counts and the relative angle between the probe and the ^{125}I(Seed).

B. Using ^{99m}Tc and ^{125}I simultaneously

We used the lower activity seed (Seed3) and ^{99m}Tc with the higher activity (Tc25) to characterize the intra-operative gamma probes on the simultaneous detection of ^{125}I and ^{99m}Tc. This is the worst scenario to localize the ^{125}I(Seed) because of the larger contribution of ^{99m}Tc in the detection of the lowest ^{125}I activity. Therefore, we assumed that by studying this situation, we could apply the conclusions to the other RTs' combinations.

- **Sensitivity:**
  The test was performed locating Seed3 and Tc20 in the same position at different distances from the probe. The results evidenced that the dependence between sensitivity and distance is the same in both cases, using only ^{125}I and adding ^{99m}Tc, as it can be seen in Fig(6). Sensitivity decreases with distance, as it was demonstrated using RTs separately. When adding ^{99m}Tc in the same localization than the seed, the variation due to the detection of the scatter radiation emitted from ^{99m}Tc, is almost negligible at visual inspection.

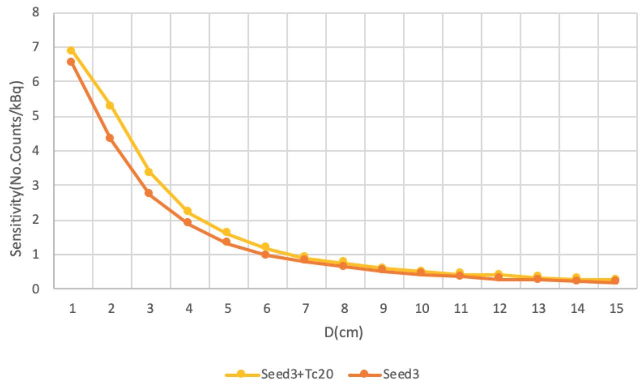

FIG. 6: Relation between the sensitivity and distance when the RTs and the probe are aligned. Measurements have been performed in the ^{125}I-channel.

- **Spatial and angular resolution:**
  Due to the complexity on performing the resolution experimental test using the two RTs simultaneously, this test was not executed experimentally and a numerical simulation was performed to study the expected effects. Knowing that the RTs detection follows a Gaussian distributions, both peaks were simulated using the results obtained from the resolution experimental test using ^{125}I and ^{99m}Tc separately (Table(II)). ^{99m}Tc peak was simulated as it was at a certain distance from the ^{125}I peak, representing the real situation where the tumour is fixed in a location and the SN's location depends on the lymphatic drainage.
  The result of the simulation is shown in Fig(7) where the tumour and the SN are separated 5cm. The centered peak corresponds to Seed3 detection and the lower one to the detection of the scattered radiation from Tc25 in the ^{125}I window. In this case, the Gaussian peaks from two RTs are distinguished if:

$$d_{12} > 2\sqrt{h_2} \tag{1}$$

  Where d_{12} is the distance between the minimum 1 and the maximum 2 and h_2 is the height of the maximum 2.
  The real distance between SN and tumour is between 5 and 15cm, therefore distinguishing the two simulated peaks following the criteria shown in Fig(7), we can conclude that the location of tumour

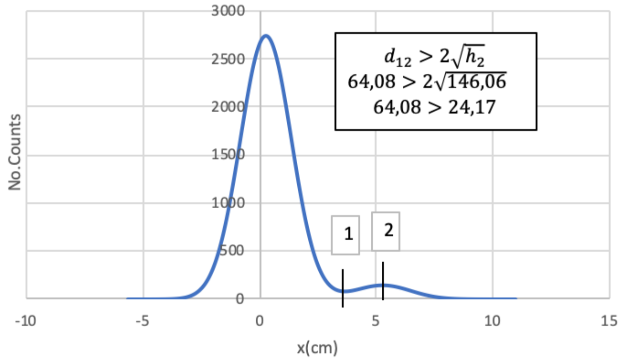

FIG. 7: Simulation of the number of counts detected based on distance from the seed (in cm), using ^{125}I and ^{99m}Tc simultaneously separated 5cm each other.

is independent of the radiation emitted from the location of SN. It has to be considered that, if the simulation is performed using a separation of 4cm it becomes impossible to distinguish the peaks and contribution between the detection appears. Anyway, is out of the interval with medical interest.

IV. DISCUSSION

Clinical observation allowed us to become aware within the medical context on the present project is based. Experimental tests using the RTs separately, allowed us to characterize the gamma probe in both detections and both channels. Having quantified the different features as sensitivity or resolution, all the technical information was provided to the nuclear medicine physician. The results obtained from directionality were unknown by the medical experts, being of significant importance to consider the maximum detection of seed's radiation when the relative angle is 90° approximately. Therefore, the physician should be aware that, during the surgical procedure, any deviation from this angle will decrease the counting rate, which not implies that the probe could be moving away from the seed.
From the results obtained from experimental test using the RTs simultaneously, we demonstrated that the excision of the tumour guided by the detection of ^{125}I(Seed) is successful and the contribution of ^{99m}Tc scatter is almost irrelevant during the surgical procedure. On one hand, we have seen that the variation on sensitivity when detecting in the ^{125}I-channel only ^{125}I(Seed) or adding ^{99m}Tc is almost negligible. Therefore, in terms of sensitivity, there is no contribution from the scatter from ^{99m}Tc. On the other hand, as regards resolution, we observed that during the detection of ^{125}I for locate the tumour, ^{99m}Tc radiation emitted from SN at the simulated distance is almost not contributing. As a conclusion, the tumour excision is based mainly on the ^{125}I(Seed) activity.

V. CONCLUSIONS

This research aimed to characterize the intraoperative gamma probes that are used in surgical procedure quantifying the sensitivity, spatial and angular resolution. Also, it was demonstrated that the directionality of the seed is a fact that it must be taken into account during the surgical procedures. Finally, the possible mutual contributions between ^{125}I and ^{99m}Tc have been demonstrated to be almost negligible during the non-palpable breast cancer surgeries. On balance, the purpose of the project is totally achieved. Once set out all the results, next step will be their validation in a clinical context during the surgical procedure.

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