Hybrid Surgical Guidance: Does Hardware Integration of γ- and Fluorescence Imaging Modalities Make Sense?

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The clinically applied hybrid tracer indocyanine green-^{99m}Tc-nanocolloid enables combined radio- and fluorescence image guidance during sentinel node (SN) biopsy procedures. To provide optimal surgical guidance, this tracer requires the presence of both γ- and fluorescence modalities in the operating room. We reasoned that the combination or integration of these modalities could further evolve the hybrid surgical guidance concept. To study this potential, we clinically applied 2 setups that included the combination of γ-detection modalities and an open surgery fluorescence camera. **Methods:** To attach the fluorescence camera (VITOM) to either a γ-ray detection probe (GP; VITOM-GP) or a portable γ-camera (GC; Vitom GC), clip-on brackets were designed and printed in 3-dimensional sterilizable RC31. Both combined modalities were evaluated in, respectively, 5 and 6 patients with penile cancer during an SN biopsy procedure using indocyanine green-^{99m}Tc-nanocolloid. Intraoperatively, radio- and fluorescence-guided SN detection rates were scored at working distances of 0, 10, 20, and 30 cm for both combinations. **Results:** Using the VITOM-GP combination, we evaluated 9 SNs. γ-tracing rates were shown to be 100%, 88.9%, 55.6%, and 55.6% at a respective working distance of 0, 10, 20, and 30 cm. Detection rates for the fluorescence imaging–based detection were found to be 100%, 77.8%, and 77.8%, at respective working distances of 10, 20, and 30 cm. When the VITOM-GC setup was used, all 10 intraoperatively evaluated SNs could be visualized with the γ-camera independent of the working distance. Fluorescence detection rates were 90%, 80%, and 80% at 10-, 20-, and 30-cm working distances. The integrated detection modalities were shown to work synergistically; overall the, GC was most valuable for rough localization (10- to 30-cm range) of the SNs, the GP for providing convenient real-time acoustic feedback, whereas fluorescence guidance allowed detailed real-time SN visualization. **Conclusion:** Our findings suggest that full integration of a fluorescence camera with γ-detector (GP or GC) can be of value when a hybrid, radioactive and fluorescent tracer is used.

Key Words: fluorescence guidance; radioguidance; hybrid modality; sentinel node biopsy; image-guided surgery

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The radioguided surgery technique has strongly evolved since its introduction in the early 1960s (*1,2*) whereby the sentinel node (SN) biopsy procedure can be considered the best-known example. Basically this technique uses a radiotracer to (specifically) label lesions that require surgical removal. In the case of SN biopsy, after the injection of a radiocolloid (often ^{99m}Tc-nanocolloid) in or around the primary tumor, on drainage of the radiocolloid through the lymphatic system the primary tumor draining lymph nodes, so-called SNs can be identified (*3*). Acoustic (and numeric) feedback generated by a γ-ray detection probe (GP) can then be used to provide directional guidance during the intervention (*4*). Alternatively, portable γ-imaging modalities can be used to provide an intraoperative image of the nodal uptake (*5,6*). Despite research-oriented efforts, commercially available portable γ-detection modalities do not yet allow depiction of detailed anatomic information (*7,8*).

To provide high-resolution optical identification of the SNs, small dyes such as patent blue (V), fluorescein, and indocyanine green (ICG) have been used (*9,10*). Unfortunately, when radiocolloids and fluorescent agents are used separately, superficial intraoperative optical findings (<1 cm) can deviate from the (in-depth) observations made using the radiocolloid (*11*). Such shortcomings can be overcome using a hybrid tracer, for example, ICG-^{99m}Tc-nanocolloid, a tracer that contains both a radioisotope and an optical fluorescent dye. The clinical value of ICG-^{99m}Tc-nanocolloid has already been extensively demonstrated by us (*12–14*) and others (*11,15*) whereby it was shown that using the hybrid tracer allows for direct translation of (in-depth) preoperative imaging findings into the operation theater. The radiolabel of the hybrid tracer allows preoperative SN mapping in a fashion similar to the conventional radioguided approach (*12*), meaning it also provides directional information for the placement of the incisions. During the operation, the combination of radio- and fluorescence guidance can be used to refine this even further by confirming the actual location and removal of the SNs defined at preoperative imaging (*12–14*). This combined approach significantly outperformed blue dye–based SN identification (*12–14*).

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The increase in the combined clinical use of radio- and fluorescence-guidance methodologies, either using separate radioactive and fluorescent tracers or using hybrid tracers, has generated a need for multiple detection modalities in the operating room. This in turn has driven the development of integrated (or rather hybrid) navigation setups wherein the fluorescence camera is positioned using SPECT-based findings (*16,17*). To date, only 1 true hybrid modality has been reported in clinical use, namely a γ-probe–based device that was extended with fiber-based acoustic fluorescence tracing capabilities (*18*). On the basis of this success, one may wonder if it is also possible to accomplish the reverse in engineering by extending a known surgical fluorescence camera technology with the ability to detect γ-rays. To this end, we combined a small-sized fluorescence camera (VITOM) (*19,20*) with a GP and a portable γ-camera (GC). Using these 2 setups, we assessed the clinical logistics during the intervention and identified the engineering challenges that needed to be resolved to make an optimal hybrid detection apparatus for clinical use.

MATERIALS AND METHODS

Hardware

Near-infrared-fluorescence imaging was performed using a lightweight fluorescence camera (VITOM; KARL STORZ GmbH & Co. KG). This open surgery camera provides real-time on-screen fluorescence images (fluorescence signal in blue) with respect to the anatomy of the patient (*20*) and enables switching between the white light and the fluorescence imaging modus.

A hand-held GP (Europrobe 2; Eurorad), providing both a numeric and an acoustic read-out, was used for intraoperative γ-tracing. A mobile GC (Sentinella; Oncovision) was used for intraoperative γ-imaging (*21*). The latter is equipped with a hand-controlled laser pointer that enables marking of the focus point/location of γ-imaging on the skin or in the wound.

Engineering of Clip-on Devices

To connect the VITOM to the GP or GC, custom clip-on brackets were designed using 3-dimensional (3D) computer-aided engineering software (Solidworks; Dassault Systèmes) and subsequently 3-dimensional printed (VDM Kunststoftechniek) in sterilizable RC31 (Envisiontec) (Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org).

The clip-on brackets were engineered in such a way that the focal points of γ-detection devices and the fluorescence camera were aligned (Fig. 1; Supplemental Fig. 1). For the fluorescence camera and γ-probe (VITOM-GP) combination, the focal point was approximately 11 cm, with an angle in alignment of both detection modalities of 7.24° (Fig. 1A). For the fluorescence camera and γ-camera (VITOM-GC) combination, the VITOM was placed under a 33.8° angle. The focal point was again localized at approximately 11 cm (measured from the tip of the VITOM) and at 6.4 cm from the collimator of the GC (9.5 cm from the detector; Fig. 1B).

Patients

Eleven patients with cT1–cT3N0 penile cancer scheduled for SN biopsy and subsequent treatment of the primary tumor were prospectively included after obtaining written informed consent. Patient characteristics are shown in Table 1.

Followed procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. This study was approved by the Institutional Review Board of The Netherlands Cancer Institute—Antoni van Leeuwenhoek hospital (NKI-AVL, Amsterdam, The Netherlands).

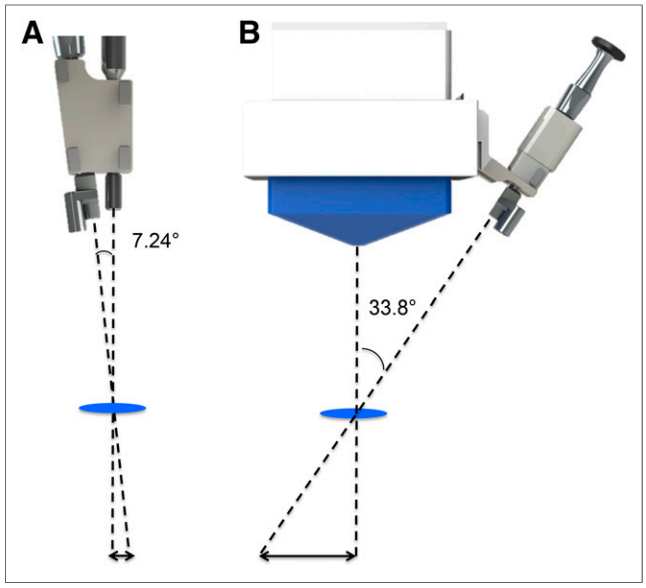

FIGURE 1. Schematic overview of VITOM-GP and VITOM-GC combination. (A) VITOM-GP combination. (B) VITOM-GC combination. Because of angle in alignment, devices had to be moved horizontally to compensate for misalignment at distances beyond focal plane.

Injection Procedure and Preoperative Imaging

Hybrid tracer injection and preoperative SN mapping were performed 1 d before surgery or on the morning of the day of surgery as previously described (*13*). In brief, 4 deposits of 0.1 mL of hybrid tracer ICG-^{99m}Tc-nanocolloid was injected per patient around the primary lesion. Dynamic (during the first 10 min after injection) and static (at 15 min and 2 h after injection) planar lymphoscintigraphy was performed. Lymphoscintigrams at 2 h after injection were followed by SPECT fused with CT (SPECT/CT) imaging. The number and location of SNs were determined on the basis of preoperative imaging and marked on the skin.

System Evaluation

The current study was performed by experienced surgical personnel that regularly uses intraoperative fluorescence- and γ-tracing modalities, even in combination with the hybrid tracer (*13*).

Before incision, the ability of the VITOM-GP or the VITOM-GC to detect the SN transcutaneously, via fluorescence imaging (*22*) and γ-detection, was evaluated when the probe was placed in direct contact with the skin (0 cm; VITOM-GP only) and at the optimal focal point (≈11 cm) of the VITOM. After tissue preparation and full exposition of the SN, the sensitivity of fluorescence imaging and γ-detection (visual or acoustic [numeric]) of the VITOM-GP and VITOM-GC was evaluated at different working distances namely: 0 (VITOM-GP only), 10 (≈VITOM focal plane), 20, and 30 cm (Fig. 2).

The efficiency of detection was scored and presented in percentage detected SNs relative to the total amount of SNs pursued (Table 1). The true value of a possible future hybrid device was evaluated in the focal plane because here both signals were detected synchronically in the same focal spot.

After SN excision, the wound bed was checked for the presence of residual radioactivity and fluorescence with either the VITOM-GC or the VITOM-GP. The SNs that were removed without evaluation of the respective hybrid modality were located with intermittent use of the GP and fluorescence detection (VITOM).

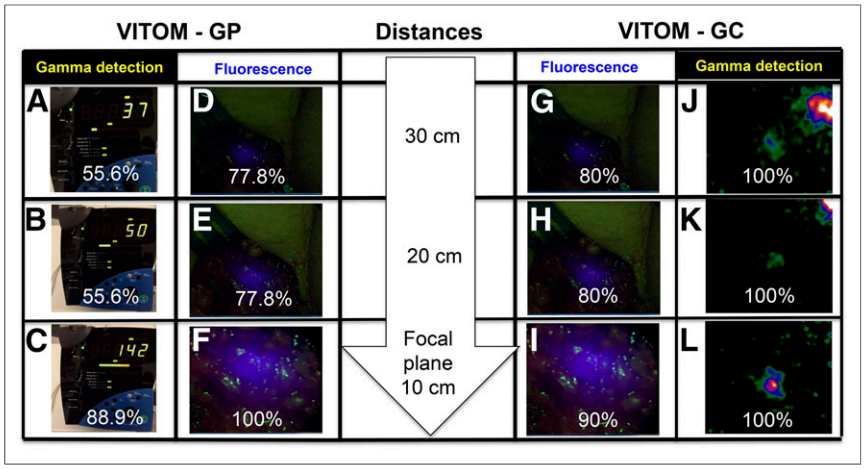

FIGURE 2. Fluorescence imaging versus γ-detection. On left side, SN detection rates (%) of VITOM-GP combination are shown in relation to the evaluated working distances (A–F). On right, SN detection rates (%) of VITOM-GC are presented in relation to the different evaluated working distances (G–L).

Pathology

Excised tissue specimens were processed as described previously (*13*).

RESULTS

Preoperative Imaging and Pathology

Details on the injected dose of the hybrid tracer, preoperative SN mapping, and pathology results are stated in Table 1.

Intraoperative Evaluation of VITOM-GP Combination

Preoperatively, 14 SNs were identified on SPECT/CT in the VITOM-GP patient group. For practical reasons, in some patients the limited available time prevented us from evaluating all SNs using the VITOM-GP combination. Therefore, only 9 of these 14 preoperatively identified SNs were included in the evaluation of the VITOM-GP combination.

Before placement of the incision, the γ-detection rate was 100% in all cases. In contrast, via fluorescence detection none of the SNs could be detected transcutaneously (Supplemental Fig. 2). Here, the VITOM was unable to fully focus at this short distance (0 cm). On SN exposure, the detection rates in the focal plane (≈11 cm from the SN) were 88.9% for the γ-detection and 100% for fluorescence detection. At 20 and 30 cm working distance, γ-tracing identified 55.6% of the pursued SNs, whereas fluorescence imaging enabled detection of 88.9% of the SNs (Fig. 2). At the larger distances, SN detection using the numeric/acoustic nature of the read-out of the GP was sometimes hindered by emissions coming from the nearby primary injection site.

The VITOM-GP combination was relatively small in size and could easily be handled with one hand. It also allowed real-time interpretation of both the γ-signal (acoustic/numeric) and the fluorescence signal (on-screen, visual). When the device was moved, the γ-tracing option provided directional feedback for the placement

TABLE 1
Patient Characteristics

Patient no.	Clinical TNM stage	Injected dose (MBq)	No. of SNs on SPECT/CT	No. of pursued SNs	No. of groins	No. of SNs at pathology	No. of tumor-positive SNs
Patients evaluated with VITOM-GP							
1	cT2N0Mx	184.28	4	3 (75%)	1	3	0
2	cT3N0Mx	77.87	2	1 (50%)	1	5	0
3	cT3N0Mx	162.74	2	3 (100%)*	1	3	0
4	cT3N0Mx	84	2	1 (50%)	1	3	0
5	cT2N0Mx	83.69	4	1 (25%)	1	4	1
Total			14	9	5	18	1
Patients evaluated with VITOM-GC							
1	cT3N0M0	143.23	3	2 (67%)	1	3	1
2	cT1N0Mx	145.37	1	1 (100%)	1	1	0
3	cT1bN0Mx	144.66	2	2 (100%)	2	2	0
4	cT2N0M0	71.62	2	2 (100%)	2	4	0
5	cT2N0M0	70.37	2	2 (100%)	2	2	0
6	cT1/2N0Mx	87.51	5	1 (20%)	1	7	0
Total			15	10	9	19	1

*Intraoperative additional SN removed.

of the VITOM-GP. As a result of the angulation of the different modalities, dual imaging was possible only at the focal point (≈11 cm). Beyond that distance, placement of the 2 modalities had to be corrected horizontally to accommodate fluorescence detection (Fig. 1).

Intraoperative Evaluation of VITOM-GC Combination

Again, for practical reasons only 10 of the 15 SNs identified using SPECT/CT were surgically pursued with the VITOM-GC combination. Before initiation of the surgical procedure the detection rate of the GC was 100%, irrespective of the evaluated working distance (10, 20, or 30 cm). Transcutaneous fluorescence-based SN detection was not possible. On SN exposure, the GC detection rate remained 100%. Fluorescence imaging provided a 90% detection rate at the focal plane, which dropped to 80% at 20 and 30 cm; in 1 patient with a body mass index over 40 fluorescence, detection failed as a likely result of tissue attenuation. When γ-imaging beyond the 20-cm distance was performed, the injection site also became visible. Other than with the GP (see above), here the GC signal could be used to aid in the orientation (Figs. 2J and 2K).

The VITOM-GC combination was large and heavy, and required a retractable (external) supporting device for placement. This device was considered convenient as it enabled accurate camera placement for longer periods of time, while leaving the surgeon's hands free to perform the resection under image guidance. The laser pointer on the GC could be used to highlight the area of interest during γ-imaging (acquisition times up to 30 s). However, as the pointer interfered with the fluorescence findings, it had to be switched off before fluorescence imaging was initiated (Supplemental Figs. 2E and 2F). Data interpretation in the focal plane was limited by the fact that both signals were visually displayed and the operating surgeon had to look at 2 screens to determine the relation between the 2 findings. Beyond the focal point, the large angle between both modalities (33.8°) meant that the spatial displacement between fluorescence- and γ-imaging findings was even more critical in this setup.

DISCUSSION

This study describes 2 hybrid imaging setups (VITOM-GP and VITOM-GC) and their potential to provide surgical guidance in combination with the hybrid tracer ICG-^{99m}Tc-nanocolloid. In both setups, the in-depth information of the γ-signal was used to determine the site of incision and provided directional guidance for positioning of the VITOM. When the SN was exposed, fluorescence imaging could be used to visually detect the SNs with respect to the anatomic context. These findings clearly underline the strengths and weaknesses of the 2 individual imaging signatures. Moreover, the reported detection percentages show that the find rates with the hybrid modality are highly similar to those previously reported for combined use of the individual modalities (*13*). The current prototype setup was not optimized from an efficacy point of view, and its use influenced operating room logistics and the operation time. More extensive future studies, however, are required to evaluate whether the use of an optimized hybrid modality can in fact result in reduced morbidity, operation time, and postoperative infection rates.

The findings of the current study allow us to derive several engineering challenges that have to be faced before imaging-based hybrid surgical guidance modalities will become efficient tools for routine use. The clip-on design was considered convenient because it efficiently combined 2 clinically available modalities but still allowed for their individual use. Unfortunately, the angled alignment was not optimal for distances smaller or larger than the focal plane. In both combined devices, the angle between the modalities dictated spatial placement to get the information from the SN for both modalities (Fig. 1). Most likely future hybrid modalities will require both modalities to be placed perpendicular to each other and with an identical field of view. Though this will require full hardware integration. The findings of the current study also suggest that placement of both image guidance modalities on a stable, but retractable, arm could be of value.

In the current setup, the optimal detection plane of the individual modalities was shown to differ for the VITOM (>11 cm), GP (0–10 cm), and GC (0–30 cm). Furthermore, intraoperative adaptation of the fluorescence focus was considered inconvenient. The concept of hybrid imaging hardware could only be accurately evaluated in the focal plane of the VITOM (≈11 cm). In future hybrid devices, the focus of the 2 modalities should be matched, at least in a certain range. Possibly an autofocus option should also be included for the optical imaging.

The largest and final hurdle to be tackled, however, will be the difference in detection sensitivity between the radioguidance and fluorescence modalities used. Although full integration is possible from an engineering point of view, its realization is not straightforward when combination of state-of-the art detector sensitivity for both fluorescence and radioactivity is envisioned. Especially when considering that the fluorescence modality could benefit from higher fluorescence sensitivity at longer distances. This would require both a stronger excitation light-source and a higher detection sensitivity. The white light option should remain included because this information created directional feedback and provided anatomic context. The difference in sensitivity between the GP and GC modalities influenced the acquisition time, collimation, and field of view (*2,6*), all of which can be improved further.

Overall the VITOM-GP combination was preferred by the surgeons over the VITOM-GC combination. The reason for this was that the acoustic/numeric feedback provided by the GP supplied information that could be processed simultaneously with the fluorescence imaging findings. Hereby 2 sensory organs, ears and eyes, work in conjunction, providing directional guidance for the placement of the fluorescence camera. In contrast, parallel display of the VITOM and GC findings relied on a single sensory organ, making it more difficult to process. Having the display of the 2 different imaging findings on 2 different screens was sometimes considered confusing. Hereby especially the lack of anatomic information in the GC images made it difficult to relate them to the fluorescence imaging findings. The value of the VITOM-GC combination could potentially increase when both imaging findings are integrated in a single (video screen) display, a technology that we previously successfully applied in a navigation setup (*23*).

CONCLUSION

In this study, we demonstrated that combined radio- and fluorescence imaging modalities have the potential to make sense in the hybrid surgical guidance concept. The integrated detection modalities were shown to work synergistically; overall the GC was most valuable for rough localization (10- to 30-cm range) of the SNs and the GP for providing convenient real-time acoustic feedback,

whereas fluorescence guidance allowed detailed real-time SN visualization.

DISCLOSURE

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