Integrating new imaging modalities in breast cancer management
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Surgical experience with intraoperative gamma cameras

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Marcel P. M. Stokkel

Clinical value and routine clinical relevance

General background
In current nuclear medicine practice, imaging is routinely performed with either conventional gamma cameras, nowadays commonly equipped with CT scanners, or with PET/CT scanners. In addition to these large devices, several intraoperative small field of view (SFOV) portable gamma cameras (PGC) have become available over the past years for intraoperative imaging. With these devices, high-resolution images of small surface areas can be obtained and local radioactivity distribution patterns can be assessed with a relative short image acquisition time. A PGC aids the surgeon to localise radioactive targets during surgery and it can also be used to guide certain interventions, such as sentinel node (SN) mapping and biopsy.

Radioguided surgery has traditionally been performed with a gamma probe to assist the surgeon to easily identify a specific target. These commercial systems are compact, easy to use and have a high sensitivity. Nonetheless, probes are collimated to a narrow FOV and only give acoustic feedback on the count-rate without offering spatial information. Indeed, PGC are known for their better spatial resolution (i.e. resolving power or ability to distinguish two hot-spots) compared to a gamma probe and provide a real-time overview of the radioactivity distribution in the imaged area. An additional benefit of surgery with a PGC is the ability to record all the consecutive steps in a procedure.

Figure 1: This is an example of a portable gamma camera; this portable gamma camera has a support system for the camera head for stable image acquisitions.
Technical features and practical considerations

Soluri and Pani patented the first PGC in 1997, called an imaging probe. [1] This camera had a field of view of 2.54 cm². Today there are several different PGC systems commercially available, such as Sentinella 102 (Oncovision, Valencia, Spain), the CrystalCam (Crystal Photonics GbmbH, Berlin, Germany), and soon the NebulEYE (Gamma Technologies Ltd, Leicester, United Kingdom). [2-4] In addition, many other PGC systems have been developed in the past, which were mainly used in clinical research settings. [5-7]

Based on the clinical experiences with these systems there are a number of practical considerations that have to be taken into account when developing a PGC system; I. it should have a sensitivity high enough to detect faint accumulation in lymph nodes, II. have the spatial resolution to distinguish between two targets, III. be adequately collimated and shielded to reduce the effects of radiation coming from the side or back, and IV. the whole system should be movable and suitable for sterile use. Since 1997 variations in camera design, technology, and functionality have been proposed. Initially, handheld gamma cameras of 1 kg or 2 kg emerged [8], followed by the generation of lighter PGC with improved ergometrical details and adequate support system for intraoperative use [3,9]. In addition to these practical specifications, the main difference between systems is the collimator design, which is either a pinhole or parallel hole configuration. The pinhole collimator enables a variable field of view, which depends on the collimator to source distance, while the parallel collimator has a fixed field of view.

![Diagram of parallel and pinhole collimators](image)

**Figure 2:** This illustration shows a schematic overview of a parallel and a pinhole collimator. The parallel collimator at the left side has a fixed field of view and the pinhole collimator field of view increases with a greater distance because of the diverging FOV.

In the Netherlands Cancer Institute, we started using PGC for radioguided surgery in 2002 with subsequent increase use for various indications [9,10]. The first PCGs were
an eZ-Scope (2002, Yokohama City University, Kanagawa, Japan) and a Minicam (2003, Eurorad SA, Eckbolsheim, France reported by Otake et al and Valdés Olmos et al.) These two models were heavy hand-held PCG devices. In 2005 a PCG, Sentinella 102, with improved ergonomic design and adequate support system for intraoperative use was introduced. This PGC was based on a Cesium Iodine (Sodium) (CsI(Na)) continuous scintillating crystal equipped with a 4mm pinhole collimator (a 2mm pinhole collimator is also available). The field of view of the pinhole camera is 4cm² when placed at 3cm from the imaging plane and increases to 20cm² when placed at a distance of 15cm. The intrinsic spatial resolution is 1.8mm, while the extrinsic spatial resolution values was 7mm and 21mm at distances of 3cm and 15cm, respectively. Detection sensitivity for the 4mm pinhole collimator depends on the distance to the imaging plane, being 319cps/MBq and 18cps/MBq for distances of 3cm and 15cm, respectively. These and other technical details of this portable gamma camera are described in more detail by Sánchez et al. [2,11]

Most PGC are suitable for detecting radionuclides with energies ranging from approximately 30keV-250keV. Their main application is the detection of ⁹⁹ᵐ-Technetium-(⁹⁹ᵐ-Tc) labelled tracers, such as ⁹⁹ᵐ-Tc-nanocolloid, with a peak radiation energy of 140.5keV. Although other tracers such as ¹¹¹-Indium, ⁵⁷-Cobalt, ¹⁵³-Gadolinium, ¹²³-Iodine, and ¹²⁵-Iodine-in the form of small implantable seeds can be easily detected, their application is less common.

**Clinical indications**

The most frequent application of PGC in our institute is intraoperative imaging to aid SN mapping and the SN biopsy in head and neck cancer, melanoma, prostate cancer, penile cancer, vulvar cancer, kidney cancer, and testicular cancer. In addition, it is also used in our hospital to monitor systemic toxicity during isolated limb chemoperfusion. The field of image-guided surgery is rapidly changing, so at the time of writing this manuscript the use of a PGC was valid for the indications mentioned above, however some of these indications may already have been replaced by new techniques in specialised centres. In the following paragraph, the results of intraoperative gamma imaging with a PGC are presented reflecting its current value in oncological practice.
Figure 3: Historical evolution of the use of portable gamma cameras at the Netherlands Cancer Institute: (a) Hand-held eZ-Scope camera with a weight of approximately 1 kg (2002) (b) Minicam with a weight of about 2 kg (2003) (c) Sentinella, the first PCG with supportive system (2005) (d) eZ-Scope used for a sentinel node procedure of the groin (2003) (e) Sentinella camera used for a laparoscopic sentinel node procedure (2006) (Courtesy of Dr. Renato A. Valdés Olmos)

Intraoperative imaging protocol

While the broad aspects of the SN procedures are similar for most indications, the details may vary per indication and institution. There are two different approaches to radioguided surgery with PGC; I. pre-surgery lymphoscintigraphy is used to place surface marks after which the PGC is used to pinpoint the exact location in the surgical field and record the entire procedure, or II. the entire procedure is performed with the PGC, thus conventional imaging is replaced by PGC-imaging before and during surgery. Though not performed in all institutes, pre-surgery lymphoscintigraphy with conventional cameras has a clear benefit especially in the assessment of more elaborate drainage patterns, such as in melanoma and head and neck cancer. [14] Subsequently, the intraoperative detection is performed by positioning the PGC close to the predefined area of interest. For the majority of image acquisitions, a 60 second acquisition time is sufficient for an adequate image. This is especially the case in SN procedures where the target to background ratio is relatively high. The system that is
used in our hospital, the Sentinella 102, enables us to project the centre of the PGC screen (i.e. central FOV) on the skin or in the surgical cavity with two intersecting laser lines. This feature allows for quick identification of the hotspots within the surgical field. At this moment, a new feature is being developed that superimposes the count data onto a real-time optical image of the surgical field, thus providing direct and intuitive translation of the imaging data into the surgical field. For SN procedures it is useful to perform additional image acquisitions after removal of each node to validate correct excision. The final post-excision image can serve as documentation to ensure correct excision of all SN.

Table 1: An overview of all PGC use in the Netherlands Cancer institute for intraoperative purposes. All of these studies are performed with the Sentinella 102.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Indication(s)</th>
<th>Patients</th>
<th>Study aim</th>
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PGC: Portable gamma camera, SN: Sentinel node
Overall results of intraoperative gamma imaging

In this section, we provide per indication a brief introduction including a short description of the procedure followed by a summary of our experience together with the accompanying reports from other centres. It has to be noted that several different approaches are valid, and that in many instances superiority of one approach over another has not been established. All studies with patients from the Netherlands Cancer Institute are tabulated to obtain a complete overview.

SN breast cancer

Currently, breast cancer is the most frequent cancer in women with nearly 1.7 million newly diagnosed cases in 2012. As in other tumours, adequate staging is required for therapy planning, and the SN procedure is regarded as standard in this respect in early-stage breast cancer. SN are defined as the first lymph nodes to receive detached tumour cells by direct lymph drainage with the potential to grow into a metastasis. In breast cancer for intratumoural tracer administrations, these nodes are located in the axilla (~86% of the cases) and/or the parasternal region (~14% of the cases). [12] Morton et al. described the first use of SN biopsies in melanoma as a less invasive technique compared to an axillary clearance and has been used now for two decades in early stage breast cancer. In an experienced multidisciplinary team, intraoperative SN identification rates of over 95% have been reported regularly. [13,14]

In 2014, around 350 SN procedures were performed in our centre out of 600 patients treated for breast cancer. Most of these procedures were performed using $^{99m}$Tc-albumin nanocolloid only, and in certain cases, in conjunction with the traditional blue dye injection. The use of blue dye depends on the surgeon’s preference and on the expected detectability of SN with the gamma probe based on lymphoscintigraphy. In 2010, a multicentre study with 52 breast cancer patients scheduled for a SN biopsy was performed. This study compared the visibility of nodes with a PGC (Sentinella 102) and a conventional gamma camera. The PGC images with a 20×20 cm field of view were acquired directly after the 2-hour post-injection static images on the large field of view camera. When lead shielding of the injection site was applied (in only 43 patients), 88% of the patients had visualisation of SN using the PGC compared to 95% with the conventional large field of view gamma camera, suggesting that the detection rate with the conventional camera is slightly better. [15] So far no additional intraoperative studies using a PGC for breast cancer SN procedures have been performed in our centre, because surgeons feel confident and achieve high success rates in locating SN
with a conventional gamma probe when good preoperative lymphoscintigraphic images are available.

Other centres have reported more extensive data on the use of PGC for SN mapping and biopsy in breast cancer. For example, Mathelin et al. described a PGC, the CarrollReS (Hitachi Chemical Co. Ltd., Japan), for SN detection and depth estimation of these nodes in breast cancer SN procedures. In the 11 patients included, the PGC visualised slightly more SN than conventional lymphoscintigraphy (respectively, 16SN and 14SN), with the benefit that it could also estimate the depth of the SN based on the Full Width Half Max of the signal with a strong correlation to the measured depth by the surgeon. [16] PGC are also used for primary breast tumour localisation in radioguided occult lesion localisation (ROLL), where $^{99m}$Tc-microaggregated albumin is injected central in the tumour, while using the Sentinella 102 or the TReCam (Bobigny University, Bondi, France). [5,17]

SN Cutaneous Melanoma

SN melanoma is, together with breast cancer, the most prevalent indication for SN procedure, as a negative SN biopsy is the most important prognostic factor for disease-free survival in stage I-II melanoma. [18] The SN procedure is generally advised in clinically localised invasive melanoma (T1b-T4b, N0 and M0). [19]

This is also the case in our centre where SN procedures for melanoma are common practice for tumour staging and optimal selection of patients before complete regional node dissection. In all cases the distribution pattern of the SN is of course related to the site of the primary tumour, and can become quite complex with visualisation of multiple SN and higher echelon nodes in several basins. In our experience, which is also underlined by other institutes, SPECT/CT imaging prior to SN biopsy is vital in difficult drainage patterns, like in the case of melanoma and head and neck cancers. [20]

In three studies performed in our institute, including a case study, the use of a PGC for SN melanoma procedures was reported. In a first study, in 3 out of 16 patients (10 melanoma head and neck area, 6 melanoma trunk) additional SN were localised with the PGC compared to the preoperative SPECT/CT scan. [21] In a second cohort of 104 patients with melanoma in the head and neck, on the trunk or extremities, the PGC was implemented as standard care in addition to preoperative lymphoscintigraphy and SPECT/CT.
The primary aim of this study was evaluation of multimodal surgical guidance using the hybrid tracer and fluorescent imaging. The clinical results of the PGC as a stand-alone device were not discussed, as it was not the research question of this study. [22]

**SN Head and neck cancer**

SN mapping for head and neck cancer in case of melanoma and Merkel cell cancer is widely used since the introduction of SN biopsies. For oral and oropharyngeal cavity cancers, predominantly squamous cell carcinoma accounting for more than 274,000 new cases annually, SN biopsies are also increasingly used as a diagnostic or staging tool. [19, 23-25] SN biopsies are indicated for clinical and radiological node negative (N0) patients with localised disease and its indication further depends on the Breslow thickness for melanoma. Nowadays mainly T1-2 tumours are included, since patients with these tumour stages are at high risk for lymph node metastases. [18, 26]

Though, the SN procedure is technically feasible in head and neck cancers with a gamma probe, it has encountered several technical challenges in terms of unpredictable drainage patterns, near injection site SN, and a highly complex and fragile anatomy within this region. [27] These challenges led to the implementation of a PGC to aid these procedures in our centre.

Our first study using a PGC in SN procedures for head and neck cancer was published in 2010 by Vermeeren et al. [28] In this study, the Sentinella was used in 25 patients with either a melanoma or oral cavity carcinoma during surgery. All SN identified by means of planar lymphoscintigraphy or SPECT/CT were also localised with the PGC. After excision of the SN the PGC was used to determine the distribution of the remaining radioactivity. In six patients the SN was identified more efficiently in terms of localisation at complex sites by the PGC and in nine patients additional SN were detected by the PGC, of which one SN was tumour positive at pathological examination.

In another study by Borbón-Arce et al., 25 patients were evaluated by a multimodality approach in which planar, SPECT/CT and PCG imaging were used. A total of 67 SN were visualised on preoperative imaging. Intraoperatively, all of these 67 SN were removed together with 22 additional nodes; 12 were located in the vicinity of the injection site during the excision and 10 SN were located by post-excision PGC imaging. [29] In a case series, it was reported that these so-called near-injection-site SN could be detected using close up imaging with a PGC, though not located with conventional planar and SPECT/CT imaging. [27] A similar conclusion was also
described in a case report where a patient with a melanoma located on the cutaneous preauricular area with preoperative non-visualisation on both planar imaging and SPECT/CT where the PGC did visualise a SN in close proximity to the injection site. [30]. The additionally localised SN can be of additional clinical value when they are the only positive nodes for the resected SN.

Nevertheless, we are not the only institute using this method for these procedures. In 2005 Tanaka et al. published a case report with the first image of a laryngeal cancer and Tsuchimochi et al. published in 2008 a series of eight patients for head and neck SN procedures, both using a different PGC than the PGC used in our centre. [31,32] In all of the nine patients all indicated SN by the conventional gamma camera were detected with the PGC.

Figure 4: Head and neck SN procedure. A 54-year-old patient with a melanoma in the neck in the right side. (a) 3D volume rendering of the SPECT/CT scan. The injection site is clearly visible and a SN at level Ia and a contralateral SN in level IV left. (b) Intraoperative imaging with a PGC, the PGC is aimed at the SN in level Ia. (c) Pre- and post-excision images with the PGC. The black-out zone used in image c1 and c2 is to shield the remaining radiation from the location of the injection site.

SN Penile cancer

The management of the regional lymph nodes is dependent on tumour-stage in penile cancer, so SN mapping and biopsy is generally performed in patients with clinically normal inguinal nodes (cN0). [33] The SN prone to metastasis are generally located at the superficial and deep inguinal node basins. In this tumour type, evaluation of both sites of the groin is performed as non-visualisation of the SN at one or both sites can result at our institute in either uni- or bilateral complete lymph node dissection (if localisation with blue dye is unsuccessful as well). Only 20-25% of the men with clinically normal nodes have regional metastasis, and therefore, a complete lymph node dissection may be overtreatment in the majority with considerable morbidity. [34] Accordingly, this can be avoided by an adequate SN mapping and biopsy procedure.
A SN with the PGC or gamma probe for early stage penile cancer is currently standard practice in our centre. In two studies described by Brouwer et al., in 2012 (9 patients) and 2014 (65 patients), a PGC was used for SN identification in penile cancer. In the first study 10 additional SN were located in 9 patients using a PGC compared to conventional detection methods including SPECT/CT. [21] In a second study two years later the PGC was used to acquire pre- and post-excision images. In 22 of the 65 patients additional nodes were depicted using the PGC compared to conventional techniques and, after the surgical area was explored once again, an additional 37 nodes were identified. [35] Consequently, a PGC is nowadays routinely used in clinical practice for all penile cancer SN procedures at our institute.

SN Vulvar cancer
As in penile cancer, a thorough evaluation of lymph nodes in the groins for optimal staging in vulvar cancer and can be considered an alternative for a complete inguinofemoral lymphadenectomy in locally advanced disease. Already in 1994, Levenback et al. introduced the SN procedure for vulvar cancer. [36] At present, the SN procedure for this indication is still used and has been reviewed as an accurate method for staging clinically and radiological node negative early stage vulvar cancer. [37] A systematic review by Selman et al. compared various approaches for detecting lymph node metastasis in women with vulvar cancer and concluded that the radiotracer procedure has a sensitivity of around 95%. [38] Therefore we incorporated this SN procedure, in our clinic and we have performed almost 100 patients SN procedures since 2012 for this indication.

In 2013, Mathéron et al. published a study on 15 patients with vulvar cancer referred for SN detection using a PGC. PGC guided the excision location and it was used for post-excision validation of complete excision. [39] In contrast with penile cancer and based on experiences of the surgeon, the PGC was not used routinely after this study for all vulvar cancer SN procedures, but only in specific cases such as poor visualisation or unclear drainage during the SN procedure. In other cases, standard probes are used with great success.

SN Prostate cancer
Although validated, but not widely used, the SN procedure for prostate cancer can be an accurate method for staging patients with a Gleason score of up to 8. [40] The main reason for the limited routine use of SN biopsy in prostate cancer is probably related to
the large variability in lymphatic drainage patterns. Also, there seems to be variation in the definitions of pelvic drainage basins in which metastatic SN can be found between institutions. In our institute, assessment of the drainage pattern of an individual patient on pre-operative imaging is an important aspect since drainage can sometimes visualise para-aortic SN nodes. [41] The surgical approach varies in terms of open and closed surgery by means of laparoscopy. Currently, we perform the SN procedure for prostate cancer on a regular base by means of laparoscopic surgery.

In different studies from our institute published in 2009, 2010 and 2011, the use of a PCG was described in this laparoscopic setting in 16, 8, 50, and 10 patients, respectively. Imaging with the PGC was performed trans-abdominal in which the position of the laparoscopic gamma probe on the screen was determined by fixing an $^{125}$Iodine seed at the tip of the probe. The radioactive seed is imaged simultaneously with $^{99m}$Tc and clearly visible on the screen of the PGC. $^{99m}$Tc is visualised as a static image and the location of the $^{125}$Iodine is repeatedly updated and visualised by a moving circle as an indicator of its location on the screen. The distance between the gamma probe tip and the $^{99m}$Tc hotspot can be determined in 2D (to our knowledge this feature is only present at the Sentinella 102). The aim of the different studies was respectively to; determine the feasibility of radio guidance during surgery, examine the para-aortic drainage patterns, optimise the colloid particle concentration, and to compare treated with untreated prostate cancer patients with regards to the drainage pattern and locations. [11,42-44]

Figure 5: Prostate SN procedure. (a) Laparoscopic gamma probe in a laparoscopic setting. (b) PGC overview image with the injection site at the bottom of the screen and 3 SN. The gamma probe tip position is indicated with the green dotted circle projected on top of the paraaortic SN.
In a large study including 55 patients the additional value of a PGC for intraoperative SN visualisation was analysed. In this study, the PGC initially visualised 16% less SN compared to SPECT/CT, but during surgery, 17 additional SN were visualised with the PGC after excision monitoring of the first SN. Two of the additionally excised SN were tumour positive lymph nodes; nonetheless, these two patients had already positive nodes in the conventionally removed SN. The main reason for non-visualisation with the PGC in the laparoscopic setting was the relatively low activity in the SN together with the relatively large imaging distance.

In 2012, a larger series of 121 patients underlined the relevance of SN locations outside the extended dissection area in patients who opt for external beam radiotherapy. In this study, the PGC was used for all patients although the description of the effectiveness of a PGC was limited, but it nicely demonstrates the level of clinical adaptation and the frequency of use for this method. Of the entire population, 31% had SN outside the standard extended dissection area, however solitary metastatic nodes within this area were rare. Still, when opting for salvage therapy, laparoscopic SN procedures are feasible.

**SN Renal cell cancer**

SN procedures for renal cell cancer are controversial and the survival benefit for these patients is still unclear. In addition, its application in this tumour type is also known to harbour a highly unpredictable lymphatic drainage pattern. Nevertheless, we do occasionally perform this procedure in T1-2 N0 patients for study purposes. In total 14 patients with renal cell cancer were operated on using a PGC for SN detection in renal cell cancer. One patient underwent laparoscopic surgery, thus the setup was similar in one patient to the previously described method where an $^{125}$Iodine seed was fixed on the laparoscopic gamma probe for probe navigation. The other cases were performed during open surgery. As the primary aim of the study was to visualise drainage patterns and it was found that the SN location was mainly in the para- and interaortocaval region. Furthermore, the feasibility of performing SN procedures for this type of procedures was demonstrated, but additional studies for this indication have not been performed as yet.

**SN Testicular cancer**

Like renal cell cancer SN procedures, testicular cancer SN procedures remain a matter of discussion. However, it is unquestionable that diagnostic techniques are needed to
assess N-stage at an early stage preventing unnecessary treatment in those without dissemination. Therefore, the SN procedure was introduced for stage I patients with testicular cancer in our hospital. [10,49] Because of its low incidence, in only nine patients undergoing surgery for testicular cancer a PGC for post-excision validation was used. In 20% of these patients additional nodes were localised by using this PGC. These results were described in three studies including respectively 2 patients, 4 patients, whereas Brouwer et al. described ultimately 9 patients in 2011 including the patients of the previous studies. [10,11,42] Testicular SN procedures as well as renal cell cancer SN procedures are relatively rare in our hospital, and therefore, a PGC can be especially helpful to ensure complete excisions and support the surgeon in making decisions.

*Isolated limb Perfusion scans*

Local treatment with high-dose chemotherapy, often tumour necrosis factor (TNF-alpha) combined with interferongamma and melphalan, of malignant melanoma or sarcoma of the limb using extremity perfusion is an elegant and effective treatment. At our institute roughly 30 isolated limb perfusion treatments are performed as a standard clinical procedure in which the PGC is used to monitor the procedure. In 2009, Orero et al. published a complete description of the procedure with a PGC and its clinical use for this indication. [50] In short, the major arteries and veins of the limb are clamped and connected to an oxygenated extracorporeal perfusion circuit, the smaller superficial vessels are clamped with a tight tourniquet. High doses of chemotherapeutical are circulated within the limb, so any leakage from this isolated blood territory can result in a high degree of systemic toxicity. [51] In this setup, a radioactive tracer, often radiolabelled serum albumin or erythrocytes, is circulated in the isolated extremity and the systemic circulating radioactivity concentration is monitored with a PGC positioned above the heart. The PGC is equipped with a specially designed flat field collimator to maximise the incoming counts, while limiting the effects of scatter from the limb. In case of a slowly increasing radioactivity concentration in the systemic blood pool an additional vessel restriction can be applied or, when the increase is too fast, the procedure should be stopped in order to avoid any systemic toxicity. [50]

**Results compared to other techniques**

Other competitive or complementary techniques do exist and facilitate the same or a similar purpose. For example, freehand-SPECT (declipseSPECT, SurgicEye GbmH, Munich, Germany) is another type of intraoperative imaging that provides additional
depth indication by a 3D reconstruction of the radioactive target lesions. Currently, different studies are performed to determine the optimal intraoperative imaging method with one of the two or with both techniques. [52,53]

A different, non-radioactive, approach is fluorescence guided imaging. Which has a very high resolution for close up imaging using fluorescent cameras, but this method lacks the possibility of preoperative imaging. To overcome this problem a hybrid fluorescent-radioactive tracer (indocyanine green $^{99m}$Tc-nanocolloid) has been introduced in our institute. This hybrid tracer is both fluorescent and radioactive and therefore allows preoperative SN imaging, real-time radio guidance, and close up high-resolution fluorescent guidance. [54] In two studies at our institute this hybrid tracer was used in head-neck surgery together with a PGC to provide excision conformance through pre- and post-excision images. The hybrid tracer demonstrated similar drainage patterns as the standard radioactive tracer ($^{99m}$Tc-nanocolloid), but also demonstrated its additional value for detecting SN situated close to injection site. [55-57] Other groups have also successfully implemented this approach for head and neck malignancies. Another important clinical application of PGC, which is not mentioned in this chapter, is its use for thyroid and parathyroid surgery; these procedures are not performed in our institute, but other institutes have shown excellent results. [58,59]

**Discussion and future applications**

Following from our previous publications the integration of PGC for complex radioguided procedures is strongly encouraged for adequate surgery. It provides pre-, peri-, and postoperative guidance by small field of view images of the targets. A concept was presented to aid successful introduction of novel techniques used for radioguided surgery. In 2011, the concept of Guided intraOperative Scintigraphic Tumour Targeting (GOSTT) was delineated by experts in this field to provide a roadmap that would optimise surgery by radio guidance. It was advised to aim for close collaborations between institutes by forming mixed networks consisting out of Universities, clinical, and commercial partners. In our experience this has been a valuable aspect in the introduction of radioguided surgery in daily clinical work. [54,60,61]

In addition to our own experience, there is an increasing number of other expertise centres using or implementing PGC for various indications. It has to be stressed that all our recent clinical results are based on just one system, the Sentinella 102. We only have limited clinical experiences with comparable systems described in technical and
clinical analyses by other centres and other systems might demonstrate different clinical results due to differences in specifications. [2,4] It is important for new users is to evaluate the needs in terms of field of view, sensitivity, image resolution, and financial plan before deciding which system would be most appropriate. We would strongly encourage a site-visit to a centre already using PGC in clinical practice to view performance in daily practice before making the final decision.

An optional feature is now available as upgrade to the Sentinella 102 enabling another hybrid approach. Optical imaging is added to the scintigraphic image for anatomical orientation. [62] In addition, a novel camera characterised by Bugby et al. uses the same hybrid approach with an integrated optical module for optical and scintigraphic imaging. [4,63,64] The hybrid approach may be beneficial for image interpretation and anatomical localisation of certain targets, but this is not as yet established yet.

Figure 6: (a) Conventional lymphoscintigraphy, an injection site with a cluster of SN cranial in this image located in the axilla. (b) Scintigraphic image acquired with a PGC. (c) Example of a hybrid image. In this image the scintigraphic image and the optical image are displayed in a single view.

For future applications we explore the possibility of replacing preoperative imaging entirely at the department of nuclear medicine by PGC imaging. Certain standardised indications, like SN procedures for primary breast cancer, could be managed using only small field of view imaging by PGC. For now, this is still in the research phase at our institute but theoretically this could drastically enhance imaging logistics before surgery. Eventually, the complete SN procedure might even (partially) be replaced by a radioguided intervention at in an outpatient setting. Imaging modalities, when adequately combined and developed, could accurately provide needle biopsy navigation towards specific targets, and thereby, circumvent surgery in specific cases. [65]

Although there are numerous publications and many encouraging developments, PGC use is not standard clinical practice in many centres. The lack of multicentre studies with large patients cohorts that prove the additional value of intra-operative PGC imaging
could be the reason for the current adaptation rate. There is still a need for evidence-based studies before the majority of hospitals would consider such an investment.

A large systemic review by Ahmed et al. published in Lancet oncology not only describes novel techniques for breast cancer SN procedures, but also points out a important obstacle for radioguided surgery; it has to be realised that currently only 60% of the eligible people have access to radioisotopes because of the complex logistics and legislation required for handling radioactive substances for medical use. [66] Therefore, novel SN localisation methods without radioactivity have been reported. SN biopsies based on microbubbles localised with ultrasonography [67], super paramagnetic iron oxide localised using a handheld magnetometer [68], and near-infrared fluorescence imaging using indocyanine green and a fluorescence camera [69] have been presented and demonstrated promising results for non-radioactive intraoperative SN localisation. [66] Disadvantages of these techniques are the lack of preoperative imaging for SN mapping; lymphoscintigraphy is able to discriminate between first echelon and second echelon nodes. MR imaging while using iron particles might solve this imaging problem but for now this would have great influence on the workload of the already frequently used MR systems. Intraoperative small field of view imaging methods for these tracers similar to PGC imaging would be a great supplement for these techniques however this is currently unavailable.

In our centre, we observe a shift from non-specific tracers towards more specific tracers. An example is radiolabelled prostate specific membrane antigen. In this way imaging and radioguided surgery are enabled towards specific target lesions. We expect that PGC could play an important role in this development by means of close up high-resolution imaging of specific lesions during surgery or interventions and preliminary studies are initiated to evaluate this concept.

**Conclusion**

PGC are known for their better spatial resolution (i.e. resolving power or ability to distinguish two hot-spots) compared to a gamma probe and provide a real-time overview of the radioactivity distribution in the imaged area. An additional benefit of surgery with a PGC is the ability to record all the different steps in a procedure. The contribution of PGC for clinical procedures is common use in our institute. For certain surgical procedures the addition of a PGC led to improved SN detection and especially aided SN localisation in complex areas such as in head and neck surgery and near...
injection site SN locations. It is expected that PGC use will increase in the future and hybrid and more targeted solutions will improve radioguided surgery even further.

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References


