

## Case Report

# Sentinel lymphonodectomy in early vaginal cancer using combined near infrared fluorescence from indocyanine green and technetium-99m nanocolloid – a first case report

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### Abstract

Nowadays, sentinel diagnostic has been made with technetium-99m-(Tc-99m)-nanocolloids as a radioactive marker and sometimes patent blue. In the last years, indocyanine green has been evaluated for sentinel diagnostic in different tumor entities. Indocyanine green is a fluorescent molecule which emits a light signal in the near infrared band after excitation. Our study aims to evaluate indocyanine green compared to the gold standard Tc-99m-nanocolloid.

We report on a patient with a unifocal vaginal cancer. Sentinel diagnostic was carried out using Tc-99m-nanocolloid, indocyanine green and patent blue. After SPECT/CT, we examined each groin for light signals from the near infrared band, for radioactivity and for blue staining. A sentinel lymph node was defined as a Tc-99m-nanocolloid positive lymph node. All sentinel lymph nodes and all additional blue or fluorescent lymph nodes were excised and tested; then sent to histologic examination.

The procedure could be accomplished without problems. We found four sentinel lymph nodes with indocyanine green fluorescence, which were positive for radioactivity from Tc-99m and therefore defined as sentinel lymph nodes. Two further lymph nodes, which showed positivity for indocyanine green signals, but not for Tc-99m were found in the left groin. The final tumor stage was pT1b, pN0 (0/6, 0/4 SLN). We saw no adverse events or complications in this patient.

Our case report shows that near infrared fluorescence deriving from ICG is a promising approach for sentinel identification in vaginal cancer. If studies using sentinel lymphonodectomy will be planned, a combined approach using Tc-99m-nanocolloids and indocyanine green could be useful.

### Introduction

Vaginal cancer is a very rare malignant disease with an incidence of 0.4 – 0.5 per 100,000 women per year. The therapeutic approach in vaginal cancer depends on the tumor stage and localization and may include a local radical excision, partial or total colectomy with paracolic tissue +/- radical hysterectomy or radiochemotherapy and / or vaginal brachytherapy [1-4]. The most important prognostic parameter in vaginal cancer is the lymphatic status of the draining lymph nodes [5-7]. In vaginal cancer, the lymphatic drainage pathways have a great variance and are depending on the tumor site in the vagina [7,8]. As a basic rule, a tumor localized in the lower third of the vagina is likely to drain in the inguinal lymph nodes like in vulvar cancer, whereas a tumor in the upper third is likely to drain into the pelvic lymph nodes like in cervical cancer.

The SLN technique in gynecologic oncology is nowadays often used in cervical and vulvar cancer [9-13]. As a complete groin dissection is associated with high morbidity like particularly lymphoedema and lymph edema, wound healing disorders and infections, sentinel lymph node (SLN) technique has been shown to reduce these significantly in vulvar cancer [9,10].

The SLN technique may lead to an optimized therapy of patients with vaginal cancer and has been successfully applied using radioactive

markers [7,14,15]. After a complete inguofemoral or pelvic lymph node dissection, the same morbidity as in vulvar or cervical cancer patients is to expect. However, the prognosis of a nodal recurrence is poor and associated with a high mortality in vulvar and cervical cancer [11,16]. The gold standard of sentinel mapping in vulvar or cervical cancer is the use of radioactive technetium-99m-nanocolloids (Tc-99m).

Near infrared fluorescence by indocyanine green (ICG) has been shown to be a promising approach for a successful SLN and resection in different gynecologic tumors [17-19]. After subcutaneous or intracutaneous injection, ICG is drained by lymphatic vessels. ICG is a fluorescence dye which has to be excited in the near infrared band at a wavelength of 807 nm and then emits a light signal of 822 nm. We present the first case report of a SLN detection using ICG in vaginal cancer.

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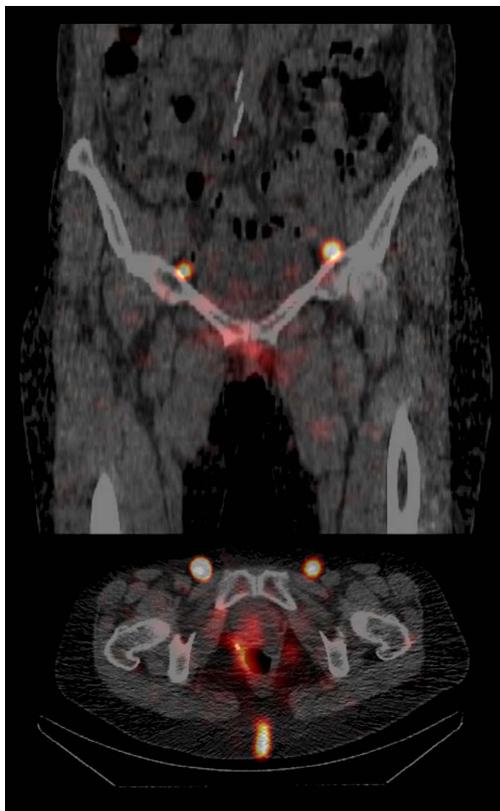
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## Patient and methods

The study protocol for using ICG in different gynecologic cancers including vaginal cancer was reviewed by the ethical committee of our institution. Written informed consent was obtained from the patient reported. The patient was a 58 year old woman with a histologically proven vaginal cancer in stage FIGO I. The tumor was located at the lower vaginal third in the rear wall with a diameter of 2 cm for the invasive lesion. The groins and pelvic lymph nodes were without suspicion of tumor infiltration by palpation, sonography and computer tomography.

A radical partial colectomy of the lower vaginal third with bilateral inguinal and / or pelvic sentinel lymphonodectomy, depending on the sentinel drainage in her case, was discussed and scheduled with the patient. Following our standard protocol for sentinel diagnostic in vulva, vaginal and cervical cancer, 10 megabecquerel (MBq) of Tc-99m-nanocolloide in 4 doses of 1 ml sterile water were injected intradermally at 4 points around the tumor site 3 hours prior to surgery. After this procedure, we performed a single photon emission computed tomography combined with conventional tomography (SPECT/CT). At this, we saw a lymphatic drainage into two inguinal SLN (Figure 1).

We dissolved a dose of 25 mg ICG (ICG Pulsion, Pulsion Medical Systems SE, Feldkirchen, Germany) in 20 ml sterile water. This leads to a concentration of 1.25 mg/ml. 4 doses of 1 ml of this solution were injected intradermally at the same injection sites as the Tc-99m injections directly before surgery (total dose of 5 mg ICG). The sentinel diagnostic and extirpation procedure was started 30 minutes after the



**Figure 1.** Single photon emission computed tomography combined with conventional tomography (SPECT/CT) from the patient showing the two inguinal sentinel sites; top: sagittal plane; bottom: transverse plane.

ICG injection, as the tumor excision was carried out first. We used an exoscopic ICG detection system (VITOM-ICG with D-Light P, Karl Storz GmbH, Tuttlingen, Germany). This system consists of a short exoscopic ICG telescope which is linked to a special camera and an image processing unit, presenting the ICG signals on a screen.

We incised the skin in the groin and searched for fluorescence accumulation in ICG detection mode in the groin using our standard procedure. The lymph nodes found by fluorescence were tested for radioactivity by Tc99m using a standard gamma probe (Neoprobe, Mammotome, Cincinnati, Ohio, USA) in vivo, than excised and tested again ex vivo. After removing all ICG-positive lymph nodes, we checked the groin for remaining Tc99m-positive, but ICG-negative lymph nodes and excised them, if present. At a last step, large palpable lymph nodes were excised, if found. All excised lymph nodes were sent separately to histological examination including ultrastaging. We closed the inguinal wounds and the vaginal wound using a lateral vulvar flap for reconstruction.

## Results

A histologically complete tumor resection could be performed. The tumor of a clinical size of 2 cm turned out to be a bifocal carcinoma with two adjacent foci of 11 mm and 5 mm. The tumor showed DNA of HPV 16. The preoperative SPECT/CT showed an inguinal lymphatic drainage in this patient, which was expected from the tumor localization. According to this, a bilateral inguinal sentinel lymphonodectomy was performed. The sentinel lymphonodectomy using ICG could be performed without problems. In the right groin, we found two neighboring lymph nodes with ICG fluorescence, which were positive for radioactivity from Tc-99m and therefore defined as sentinel lymph nodes. No other ICG- or Tc-99m-positive lymph nodes were found in this groin (Figure 2).

In the left groin, we located two neighboring lymph nodes with ICG fluorescence, which were positive for radioactivity from Tc-99m, too. After excision of these lymph nodes, we found another lymph node, which showed positivity for ICG signals, but not for Tc-99m. This lymph node was excised, too, and sent to histologic examination separately.

Histologic review including ultrastaging revealed two sentinel lymph node without tumor infiltration from both sides; the ICG-positive, Tc-99m negative lymph nodes turned out to be another two lymph nodes free of tumor infiltration. Therefore, the final tumor stage was pT1b, pN0 (0/6, 0/4 SNL), G2, L0, V0, R0. We saw no adverse events or complications in this patient. The postoperative course was uneventful.

## Discussion

This is the first report of a successful SLN dissection using near infrared fluorescence from ICG in vaginal cancer. All sentinel lymph nodes which were positive for Tc-99m-nanocolloide as the actual gold standard were positive for ICG, too. We found two additional ICG-positive-, but Tc-99m-negative lymph nodes in the left groin. There is only limited data about the sentinel technique in vaginal cancer. Hertel *et al.* [7] from our institution published 7 cases with successful sentinel detection using Tc-99m, patent blue and SPECT/CT. Pelvic sentinel lymph nodes were detected in the 6 patients with infiltration of the middle or proximal vaginal third. In one patient with the tumor site in the lower third, inguinal sentinel lymph nodes were found [7]. Frumowitz *et al.* [14] reported 5 cases of sentinel detection in vaginal cancer using 37 MBq of Tc-99m and could successfully detect sentinels

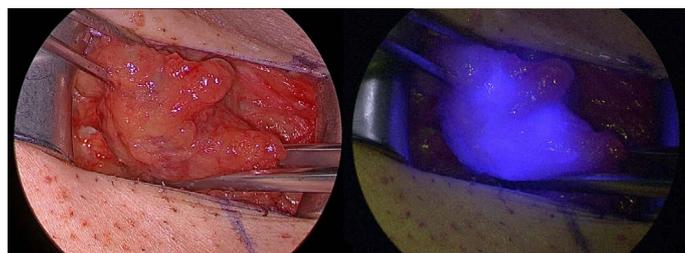
in all cases. Van Dam *et al.* [15] showed a successful sentinel detection in further 4 cases using Tc-99m, too [15].

As ICG is not bound to a nanocolloid, the molecule is evacuated gradually through the lymphatic system. If the time between injection and detection is long, a complete fluorescence lymphography of the inguinofemoral lymph system will be the result. In our case, this probably led to the marking of 2 further non-sentinel lymph nodes in the left groin (as the right groin was treated before the left groin). One method to overcome this disadvantage would be to bind ICG to albumin or other nanocolloids which has been described in several smaller studies in vulvar or cervical cancer [20,21]. In vaginal cancer, a preoperative SPECT/CT or a lymphoscintigraphy is very important, as the lymphatic drainage can vary between pelvic and inguinal lymph sites, especially when the tumor localization is in the middle third of the vagina [7]. Therefore, marking with a radioactive marker should be performed with a radioactive marker in every case of vaginal cancer. But ICG has additional value in the sentinel marking. Using ICG, a visual dimension is added to the sentinel detection, so that the surgeon does not have to change between the gamma probe and surgical instruments to remove the sentinel lymph nodes. This may provide a better comfort for the surgeon. Furthermore, there is a special advantage of ICG fluorescence detection in the groin: While identifying the sentinels with the gamma probe in the groin, the probe is usually directed from laterocranial to mediocaudal which often leads to a disturbing gamma signal from the injection field at the vagina or vulva. Using ICG, this problem can be circumvented, as the ICG fluorescence shows directly the sentinel lymph nodes (Figure 3).

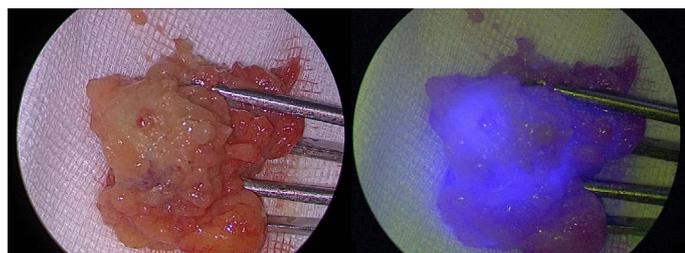
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**Figure 2.** Right groin with sentinel lymph node under white light inspection (left) and in the near infrared fluorescence mode.



**Figure 3.** The same sentinel lymph node ex vivo under white light inspection (left) and in the near infrared fluorescence mode.

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