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Surgery in Motion

A Hybrid Radioactive and Fluorescent Tracer for Sentinel Node Biopsy in Penile Carcinoma as a Potential Replacement for Blue Dye

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Abstract

Background: Sentinel node (SN) biopsy in penile cancer is typically performed using a combination of radiocolloid and blue dye. Recently, the hybrid radioactive and fluorescent tracer indocyanine green (ICG)-^{99m}Tc-nanocolloid was developed to combine the beneficial properties of both radio-guidance and fluorescence imaging.
Objective: To explore the added value of SN biopsy using ICG-^{99m}Tc-nanocolloid in patients with penile carcinoma.
Design, setting, and participants: Sixty-five patients with penile squamous cell carcinoma were prospectively included (January 2011 to December 2012). Preoperative SN mapping was performed using lymphoscintigraphy and single-proton emission computed tomography supplemented with computed tomography (SPECT/CT) after peritumoural injection of ICG-^{99m}Tc-nanocolloid. During surgery, SNs were initially approached using a gamma probe, followed by patent blue dye and/or fluorescence imaging. A portable gamma camera was used to confirm excision of all SNs.
Surgical procedure: Patients underwent SN biopsy of the cN0 groin and treatment of the primary tumour.
Outcome measurements and statistical analysis: The number and location of preoperatively identified SNs were documented. Intraoperative SN identification rates using radio- and/or fluorescence guidance were assessed and compared with blue dye. Statistical evaluation was performed using a two-sample test for equality of proportions with continuity correction.
Results and limitations: Preoperative imaging after injection of ICG-^{99m}Tc-nanocolloid enabled SN identification in all patients (a total of 183 SNs dispersed over 119 groins). Intraoperatively, all SNs identified by preoperative SN mapping were localised using combined radio-, fluorescence-, and blue dye guidance. Fluorescence imaging enabled visualisation of 96.8% of SNs, while only 55.7% was stained by blue dye ($p < 0.0001$). The tissue penetration of the fluorescent signal, and the rapid flow of blue dye limited the detection sensitivity. A tumour-positive SN was found in seven patients.
Conclusions: ICG-^{99m}Tc-nanocolloid allows for both preoperative SN mapping and combined radio- and fluorescence-guided SN biopsy in penile carcinoma patients and significantly improves optical SN detection compared with blue dye.

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1. Introduction

Penile carcinoma predominantly shows metastatic spread via the lymphatic system. As a consequence, lymph node (LN) staging in penile carcinoma has strong prognostic implications [1]. Since only 20–25% of patients have regional metastases, performing a complete LN dissection (LND) may be overtreatment, resulting in considerable morbidity [2]. Sentinel node (SN) biopsy is a validated procedure to detect (micro)metastases in clinically node-negative groins without the morbidity associated with a complete LND. Yet the reliability of SN biopsy depends on successful pre-, intra-, and postoperative identification of all (tumour-positive) SNs [3,4].

Generally, SNs are preoperatively identified using lymphoscintigraphy after peritumoural injection of a radioactive tracer (^{99m}Tc-nanocolloid is the gold standard in Europe). With the introduction of single-photon emission computed tomography supplemented with computed tomography (SPECT/CT), it has become possible to detect the SNs in their anatomic context [5]. This three-dimensional (3D) information can be used to accurately plan the surgical approach.

The intraoperative procedure traditionally relies on localisation of the radioactive signal using a handheld gamma ray detection probe (hereafter referred to as gamma probe) that generates an acoustic readout. A portable gamma camera has been introduced with the ability to acquire intraoperative overview images of radioactive hotspots. Unfortunately, the current portable gamma cameras are unable to provide adequate anatomic information, leaving the radioactive signal depicted against a two-dimensional black background [6]. To anatomically visualise the SNs within the surgical field, a second injection with blue dye is usually administered shortly before surgery. However, one of the disadvantages of blue dye is that preoperatively defined (radioactive) SNs may not always be stained blue at the time of excision [7]. Moreover, blue dyes stain the injection site, potentially hindering the tumour resection, which is generally performed after SN biopsy.

The use of near-infrared (NIR) fluorescence imaging has characteristics that can be advantageous for intraoperative SN detection: an improved tissue penetration compared to blue dye, and the fluorescent signal is only visible using a dedicated NIR fluorescence camera system, leaving the surgical field unstained [8]. Similar to blue dye, fluorescence imaging normally also requires an additional injection of, for example, the clinically approved indocyanine green (ICG). Like blue dye, ICG migrates quickly through the lymphatic system, resulting in a limited diagnostic window. The larger radioactive ^{99m}Tc-nanocolloid does not have this limitation [9].

To combine the beneficial properties of both radio guidance and fluorescence imaging, ICG-^{99m}Tc-nanocolloid was developed [9,10]. This hybrid tracer expands the gold standard radiotracer ^{99m}Tc-nanocolloid with an NIR fluorescent component (ICG) without altering the well-validated tracer kinetics of the gold standard [11]. Pilot studies have demonstrated the feasibility of this hybrid approach in head and neck malignancies and prostate cancer [12–14]. Its added value, however, remains to be assessed in a more extensive study population. The purpose of this study was to evaluate the added value of SN biopsy using ICG-^{99m}Tc-nanocolloid compared with blue dye in a large cohort of patients with penile carcinoma.

2. Methods

2.1. Patients

A total of 84 consecutive patients presenting with ≥T1G2 tumours were prospectively included. The SN procedure was performed following the European Association of Urology penile cancer guidelines [15]. The study protocol was approved by the institutions' medical ethics committees (N09DRF, NL 26699.031.09).

Seventeen patients were excluded from the study. Nine patients were previously included in a reproducibility study [11]. In five patients, excised SNs were only evaluated ex vivo. In one patient no blue dye was used; one patient presented with a penile melanoma; and another patient presented with a carcinoma of the urethra.

Characteristics of the remaining 65 evaluated patients are listed in Table 1. Only patients with at least one cN0 groin were enrolled. In patients with proven unilateral nodal involvement (n = 10) or with a previous unilateral LND (n = 1), only the contralateral cN0 groin was included for SN biopsy, resulting in a total of 119 included groins. Patients were scheduled for SN biopsy or repeat SN biopsy (n = 6) in case of a recurrent tumour, followed by treatment of the primary tumour or for SN biopsy only in case of previous penile surgery in another centre.

2.2. Tracer preparation

ICG-^{99m}Tc-nanocolloid was prepared as previously described [11]. Subsequently, approximately 90 MBq ± 10% was subtracted from the vial containing the ICG-^{99m}Tc-nanocolloid solution. Saline was then added to reach a total volume of 0.4 ml in the syringe. All procedures were performed under good manufacturing practice and under supervision of the institution's pharmacist.

2.3. Preoperative procedure

A schematic overview of the study setup is given in Figure 1. ICG-^{99m}Tc-nanocolloid was intradermally injected proximally around the tumour in three or four deposits on the same day or on the day before surgery. No adverse reactions were observed.

Dynamic lymphoscintigraphy was performed during 10 min immediately after injection, using a dual-head gamma camera (Symbia T;

Table 1 – Patient characteristics

Included patients, no.	65
Age, yr, mean (range; median)	67 (34–93; 66)
Recurrence (repeat SN biopsy), no.	6
Tumour stage, no.	
T1	25
T2	34
T3	6
Groins, no.	
cN0 (with or without) FNAC	119
cN1 (tumour + FNAC)	10
Previous LND	1
Total included groins for SN biopsy	**119**

SN = sentinel node, FNAC = fine-needle aspiration cytology, LND = lymph node dissection.