The use of indocyanine green for accurate sentinel node detection and removal in a group of high-risk nodal metastasis prostate cancer patients
To optimize and improve the sentinel node procedure in men with prostate cancer

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The overall goal of this study is to further validate and improve the sentinel node procedure for prostate cancer using ICG-99mTc-nanocolloid. The first objective aims at further validation of the sentinel node procedure for prostate cancer via...

Ethical review	Approved WMO
Status	Pending
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON44119

Source
ToetsingOnline

Brief title
Optical sentinel node detection in prostate cancer

Condition

- Reproductive neoplasms male malignant and unspecified
- Prostatic disorders (excl infections and inflammations)

Synonym

prostate cancer, prostate carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Intuitive Research Grant

Intervention

Keyword: lymphnode, prostate cancer, sentinel node

Outcome measures

Primary outcome

Primary objective: Further validation of the sentinel node procedure for prostate cancer via ultrasound guided transrectal ICG-99mTc-nanocolloid injection surrounding the tumor tumor location will be determined following diffusion weighted MR imaging.

Secondary outcome

Secondary objective: Improving the ICG-99mTc-nanocolloid injection; an ultrasound guided intratumoral injection of ICG-99mTc-nanocolloid will be performed instead of a transrectal injection

Tertiary objective: Improving the identification of lymphatic drainage patterns through a preoperative intraprostatic injection of fluorescein at the start of the surgical procedure. This fluorescein injection will be given to patients who also received an intratumoral injection of ICG-99mTc-nanocolloid in the morning (a total of 20 patients will be included that have already been included under the secondary study objective).

Quaternary objective: Fluorescence imaging of paraffin-embedded prostate

samples

allows the determination of the tumor location with regard to the location of

the ICG-99mTc-nanocolloid deposits

Study description

Background summary

Presence of metastasis in the first tumor draining lymph node(s) (referred to as
sentinel node) in the pelvic region is considered a strong predictor of treatment failure in patients with prostate cancer [Fujisawa, 2008 #2]. Postoperative histopathological examination of tissue samples obtained during surgery is the *golden standard* to assess the metastatic spread. To obtain these samples, extensive dissection of the lymphatic tissue is required, a procedure that can lead to post-operative complications such as lymphoceles, injuries to the obturator nerve and/or the ureter, and lymphedema of the lower extremity [Heidenreich, 2007 #3]. Moreover, despite an increase in resected lymph nodes, early sentinel node studies have indicated locations of primary landing sites outside the extended field in 5-10% of cases.
Surgical pelvic lymphadenectomy can be improved with better surgical guidance along the (tumor draining) lymphatic ducts towards the (sentinel) lymph nodes [Jeschke, 2008 #1;Link, 2001 #4;Bader, 2002 #6]. Ideally, an intraoperative imaging approach enables the surgeon to visualize and excise these sentinel nodes accurately, which may shorten overall procedure time and decrease complication levels.
Innovations in lymph node mapping have come mainly from the melanoma and breast cancer fields [Giuliano, 1994 #7;Morton, 2006 #8]. At present, lymph node mapping in e.g. the breast is performed with a combination of preoperative 99mTc-labeled nanocolloid injection and intraoperative injection of blue dyes (e.g. patent blue) for visible guidance [Mariani, 2004 #13].
Preoperative lymphoscintigraphy, using 99mTc-labeled nanocolloidal particles, has also demonstrated its use in imaging of the sentinel nodes in the prostate [Warncke, 2007 #15]. The intraoperative translation of the radiocolloid procedure requires the use of a gamma probe or camera to monitor the transit of a 99mTc-labeled nanocolloid from the injection site into the sentinel node(s) (currently used in the clinic at the NKI-AvL) [Meinhardt, 2008 #17;Olmos, 2009 #20]. Unfortunately, the applicability of radionuclide-based intraoperative detection remains challenging. Ideally an extra visual aid, e.g. blue dyes, can help guide the surgeon. However, the dynamics of the conventional blue dye

limit
its use in prostate cancer.
Recently, several promising new trials have been published for breast, prostate,
and gastrointestinal cancer [Ogasawara, 2008 #22;Kusano, 2008 #25] using the near-infrared (NIR) fluorescent dye indocyanine green (ICG) for intraoperative fluorescence detection of lymph nodes. In a feasibility study (in breast), the federal drug administration (FDA) has suggested that a *cocktail* injection of fluorescent and radioactive agents would be preferable over multiple single injections [Sevick-Muraca, 2008 #26]. In the preclinical setting we have fully optimized this approach in a spontaneous mouse model for prostate cancer [van Leeuwen, 2011 #40].
In the previous version (version 1.1) of this study protocol, we performed a pilot study using a combination *cocktail* of ICG and 99mTc-nanocolloid (hereafter referred to as ICG-99mTc-nanocolloid) for sentinel node mapping during laparoscopic pelvic sentinel node dissection for prostate cancer. Here we
showed that with ICG-99mTc-nanocolloid we were able to facilitate and optimize dissection of the sentinel nodes during robot-assisted laparoscopic prostatectomy (RALP) procedures [van der Poel, 2011 #39]. ICG-99mTc-nanocolloid allowed preoperative surgical planning and intraoperative optical detection of the sentinel nodes. Furthermore, it was found that especially when sentinel nodes were located close to the injection site, fluorescence imaging was useful as gamma probe detection was hindered due to the background signal coming from the injection site [van der Poel, 2011 #39]. In addition to this, the fluorescence signal (which can be detected > 3 months after injection) allowed us to study the influence of the location of the intraprostatic injections on the observed lymphatic drainage [Buckle, 2012 #129]. Fluorescence imaging of the
paraffin-embedded prostate samples suggested that the location where the tracer is injected is of influence on the observed lymphatic drainage pattern [Buckle, 2012 #129].

Study objective

The overall goal of this study is to further validate and improve the sentinel node procedure for prostate cancer using ICG-99mTc-nanocolloid. The first objective aims at further validation of the sentinel node procedure for prostate cancer via ultrasound guided transrectal ICG-99mTc-nanocolloid injection surrounding the primary tumor. To achieve this goal, tumor location will be determined based on the acquired diffusion weighted MR images.

Secondly, in a subset of 20 patients we would like to study whether we can improve the identification of lymphatic drainage patters through a preoperative intraprostatic injection of fluorescein at the start of the surgical procedure.

Tertiary objective: Fluorescence imaging of tracer deposits in paraffin

embedded prostate tissue

Study design

This is a non-randomized, open study on the use of ICG-99mTc-nanocolloid to improve the sentinel node procedure of prostate cancer. The addition of fluorescence (ICG) to the conventional (99mTc-nanocolloid) sentinel node procedure allows intraoperative optical detection of the sentinel node thereby possibly improving the sentinel node procedure as a whole. Fluorescein is used to visualize tumor draining lymphatic ducts during surgery.

Study population:
A total of 112 patients will be included in this study with localized prostate cancer.

Intervention

No special patient preparation is required. Approximately 4 hours prior to surgery ICG-99mTc-nanocolloid will be injected transrectally under ultrasound guidance into the prostate tumor as is routinely done for 99mTc-nanocolloid guided sentinel node detection. Patients will undergo lymphoscintigraphy and a SPECT/CT scan for preoperative planning. To answer the tertiary objective, 5-10 min prior to surgery, in a subset of 20 patients, fluorescein will be injected into the prostate. During surgery the resection will be guided by both the radioactive signature (laparoscopic gamma probe) and the fluorescent signature (fluorescence laparoscope (Karl Storz Endoscopes)).

Study burden and risks

Other than intraoperative injection and tracking of ICG (and fluorescein), this study will not be any different from standard procedures. ICG-99mTc-nanocolloid will be injected approximately 4 hours prior to surgery. Additionally, in a group of 20 patients, prior to surgery fluorescein will be injected. Operation time may be extended by 10-15 min due to the imaging time. It may, however, be anticipated that the number of resected sentinel nodes, and hence staging, may be improved after ICG-99mTc-nanocolloid (and fluorescein) injection.
As mentioned earlier, in rare cases oversensitivity (> 1/1.000 to < 1/100 (fluorescein)), nausea, urticarial and anaphylactic reactions (< 1/10.000 (ICG);
> 1/10.000 to < 1/1.000 (fluorescein)) have been reported after intravenous injection of ICG or fluorescein. Because of the proposed exclusion criteria, these numbers will be lower within this study. Patients will be monitored up to 24 hours post-surgery.
Conversely, the value of adequate lymphadenectomy could have major results on the improvement of staging and postoperative outcome of prostate carcinoma

patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Histologically proven prostate cancer
* Increased risk of nodal metastases according to the MSKCC nomogram (> 10%)
* Scheduled for surgical (laparoscopic) prostatectomy including nodal dissection

Exclusion criteria

* History of iodine allergy

* Hyperthyroid or thyroidal adenoma
* Kidney insufficiency

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2012
Enrollment:	112
Type:	Anticipated

Ethics review

Approved WMO Date:	27-03-2013
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-11-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-03-2014

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-01-2016
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL41285.031.12