A phase II validation of in vivo Raman spectroscopy for bladder cancer diagnosis

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Primary Objective:to clinically use and validate the optimized Raman probe in a patient database in order to differentiate between benign and malignant bladder lesions in vivo.Secondary objective:to develop an algorithm to predict tumor grade in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON35830

Source
ToetsingOnline

Brief title
Raman Spectroscopy in Bladder Cancer Diagnosis

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
bladder cancer, urothelial cell carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: bladder cancer, optical biopsy, Raman spectroscopy

Outcome measures

Primary outcome

To differentiate between benign and malignant tumor in the bladder using in

vivo Raman spectra for bladder cancer diagnosis

Secondary outcome

To determine grade and stage using in vivo Raman spectra for bladder cancer

diagnosis

Study description

Background summary

Bladder Cancer Epidemiology
Bladder cancer is a significant public health problem responsible for more than 130,000 deaths annually worldwide. It represents the fourth most common cancer in men and the 8th most common in women for a 3:1 male predominance. Bladder cancer is a malignant neoplasm originating from the surface lining (mucosa) of the bladder. The most common form is urothelial cell carcinoma (UCC) which accounts for 90-95% of all bladder cancers. The remainders are squamous cell carcinomas (3-7%), adenocarcinomas (1-2%).

Disease presentation
When cancer is limited to the mucosa of the bladder it is referred to as "superficial", mainly defined by its appearance at surgical cystoscopic removal rather than its intrinsic invasive potential. Approximately 70% to 80% of patients with newly diagnosed bladder cancer will present with superficial bladder tumors. Those who do present with superficial, noninvasive bladder cancer are often curable. Patients in whom superficial tumors are less differentiated, large, multiple, or associated with carcinoma in situ (CIS) in other areas of the bladder mucosa are at greatest risk for recurrence and the development of invasive cancer. Such patients may be considered to have the entire urothelial surface at risk for the development of cancer. Early diagnosis and complete resection of tumor lesions is essential to bring a change in prognosis for those with CIS and high grade neoplasms in particular.

Current Diagnostic Methods

The gold standard in diagnosis for bladder cancer is a selection of the region of interest by ordinary white light cystoscopy and pathological assessment of biopsies from selected lesions of the bladder wall. In case of non-muscle invasive cancer, the treatment strategy is to eradicate existing disease, prevent tumor recurrence and avoid development of invasive disease. To prevent tumor recurrence, adjuvant intravesical (immuno- or chemo-) therapy (IVT) with use of various drugs is used to destroy viable tumor cells. The high recurrence rate may be due to overlooked and or incompletely removed lesions related to the diagnostic assessment by white light cystoscopy. Photodynamic diagnosis (PDD) is a kind of fluorescence guided resection during cystoscopy. It was introduced in urology as a modality that would enhance visual contrast of normal versus tumor tissue of the bladder and enhances the diagnostic value of cystoscopy. However despite the increase in sensitivity this contrast enhancement has been received with skepticism because of its lack in specificity due to more false positive lesions.

Raman spectroscopy

Raman spectroscopy is a molecular specific technique that can be used as a biochemical tool to study different (biological) materials; in particular this technique has the capability to provide differential diagnosis of pre-cancers and cancers.

An in vitro study was performed by Crow et al. to determine the sensitivity and specificity of Raman spectroscopy. Bladder samples collected during cystoscopic procedures were snap-frozen and a section was taken for histological examination. Samples were classified as normal, cystitis, carcinoma in situ (CIS), urothelial cell carcinoma and squamous cell carcinoma (SCC). In 76 patients, 1685 spectra were recorded (590 benign and 1095 malignant spectra). These spectra were analyzed using principal-component fed linear-discriminant analysis (PCA/LDA), to construct a diagnostic algorithm. The algorithm was tested for its accuracy in predicting the histological diagnosis. The accuracy achieved by the algorithm for normal, cystitis, CIS, TCC and SCC, were respectively (sensitivity), 91%, 79%, 86% and 84%, and 98% and (specificity) 96%, 92%, 97%, 96% and 100%.

Raman spectroscopy and Photodynamic Diagnosis

Raman spectroscopy is a highly specific technique, but suffers from lack of screening possibilities with respect to the surface area assessed (order of magnitude square cm). Photodynamic diagnosis (PDD) of bladder cancer enables gros evaluation of the bladder wall surface with high sensitivity (97%), but relatively low specificity (50%)16, 28. Therefore, a combination of PDD and Raman spectroscopy, may enable optical diagnosis at the lesion of interest and would enhance the specificity and efficacy for early bladder cancer diagnosis. An in vitro study of Raman spectroscopy of bladder wall samples after fluorescence image guided biopsy showed the feasibility of the combination of these
techniques.

Our group investigated the combination of Raman spectroscopy and PDD in a retrospective study. Patient groups were identified who are associated with an increased number of false positives in fluorescence diagnosis and would therefore benefit most from the addition of Raman spectroscopy. Multivariate analysis showed that female patients and patients who have had a recent TURBT, within 12 weeks before PDD, would benefit most form highly specific Raman spectroscopy because recent TURBTs and female gender are significant independent predictors of fals positive findings in PDD.

Rationale for differentiation between benign and malignant, grade and stage
Application of Raman spectroscopy in pre-clinical and clinical diagnosis in preliminary research, has shown that algorithms are not one-to-one interchangeable in translation from an in vitro to an in vivo situation. This is caused on one hand, by the sensitivity of this technique for subtle biochemical changes and on the other hand, the biochemical difference of biopsies of the same tissue in vivo. Nevertheless the result of patient measurements can be compared between the patients diagnosed with use of PDD and white light, with some adjustments.The preliminary study phase I "Determination of instrument parameters for the in vivo application of Raman spectroscopy for Bladder Cancer Diagnosis" showed that spectra with enough signal/noise ratio can be obtained in a clinical setting in vivo. Furthermore a correlation of the Raman signal and the invasion was determined. Further differentiaton of subgroups requires more research.

Study objective

Primary Objective:
to clinically use and validate the optimized Raman probe in a patient database in order to differentiate between benign and malignant bladder lesions in vivo.

Secondary objective:
to develop an algorithm to predict tumor grade in exophytic and flat lesions

Tertiary Objective:
to develop an algorithm to predict tumor stage in exophytic or solid lesions by accurate prediction of the depth of invasion.

Study design

This study will be performed in the UMC Utrecht and Sint Antonius Hospital in Nieuwegein. 285 patients will be included, who are sceduled for a TURBT by standard medical care.

Intervention study: This concerns an experimental study to determine a differentiation between benign and malignant bladder lesions, using in vivo Raman spectroscopy in bladder cancer detection.

All subjects are measured at the time of the procedure; after selection of regions as determined by standard medical diagnostics. In each patient the acquisition time is 3 seconds per measurement. A database of patient measurements will be produced. Using data-analysis, spectral differentiation between benign and malignant is conducted as well as between different grades and stages.

First objective:
- benign
- malignant

Second objective:
To grade :
- flat lesions
o normal
o inflammation
o pre-malignant (hyperplasia, atypia and dysplasia)
o Carcinoma In Situ (CIS)
- exphytic lesions
o grade 1
o grade 2
o grade 3

Third objective:
To stage:
- non-invasive Ta (NMI-BC)
- superficial invasion T1 (NMI-BC)
- muscle invasion T >= 2 (MI-BC)

The Raman spectroscopic diagnoses are compared to the pathologic diagnoses of 285 patients from the UMC Utrecht and the Sint Antonius Hospital.

Study burden and risks

The extent of the burden for the patient in this study is limited to an extension of the surgical procedure time in the operating room. The standard assessment of the disease by visual evaluation of the bladder wall is carried out regularly. Suspicious regions selected for biopsy then are recorded on a form designed for this purpose. When present, lesions that are expected to be normal, deviant benign and/or malignant are selected for Raman spectral measurements. At each location multiple measurements are taken with acquisition times of 3 seconds and use of two different probes, to determine differentiation between benign and malignant, grade and stage using in vivo Raman spectroscopy in the bladder. The extension in time to the procedure will not exceed 15 minutes. A minimal increase in risk for damage of the bladder wall considering the increase in instrument manipulation time in the urinary

bladder is the additional risk.
Another additional risk in this procedure might be that an extra biopsy is being taken from healthy mucosa which might lead to bleeding in the bladder. Nevertheless, during a TURBT procedure, the bleeding can be stopped by electrical coagulation which is used regularly during a TURBT.

Risks of a surgical procedure: pain, infection, scarring, bleeding.
Risks of anesthesiology: hypersensitivity of medicins, respiratory arrest, cardiac arrest. The risks during local anesthesiology are minimal.

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

Subjects (at least 18 years old and mentally competent) that present with bladder cancer

symptoms at the outpatient clinic and are scheduled for transurethral resection of tumor or biopsy (TURTB) are candidates for recrution

Exclusion criteria

Subjects scheduled for TURBT that present with macroscopic hematuria at the time of procedure are excluded from the study as the excess of blood in urine complicates the cystoscopic guidance to sites and affects the Raman spectra.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-03-2013
Enrollment:	285
Type:	Actual

Medical products/devices used

Generic name:	Raman probe
Registration:	No

Ethics review

Approved WMO

Date:	31-08-2011

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-10-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL35581.041.11