Clinical trial results:
Accuracy of lymph node imaging in prostate cancer: A prospective cohort study to determine the concordance between two imaging modalities, “Combidex” magnetic resonance imaging (Nano MRI) and 68Ga-PSMA positron emission tomography (PET).

Summary

EudraCT number	2015-005016-15
Trial protocol	NL
Global end of trial date	30 October 2017

Results information

Result version number	v1 (current)
This version publication date	30 October 2024
First version publication date	30 October 2024

Trial information

Trial identification

Sponsor protocol code	NL55589.091.16

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03223064
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboudumc
Sponsor organisation address	Geert Grooteplein Zuid 10,, Nijmegen, Netherlands,
Public contact	Radiology and Nuclear Medicine, Radboudumc, 0031 243615105, trialbureau.radng@radboudumc.nl
Scientific contact	Radiology and Nuclear Medicine, Radboudumc, 0031 243615105, trialbureau.radng@radboudumc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 October 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2017
Global end of trial reached?	Yes
Global end of trial date	30 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aimed to evaluate the effectiveness of ePLND in removing metastatic LNs in men with primary intermediate and high-risk prostate cancer and assess the value of nMRI and PSMA-PET/CT in detecting small metastatic LNs.

Protection of trial subjects:

Both 68 Ga-PSMA-PET/CT and Nano-MR Lymphography (Ferumoxtran-10) have been used for over 5 years for the detection of metastases in patients with prostate cancer at intermediate to high risk. Pelvic Lymph Node Dissection and image directed dissection can be considered as the gold standard for such patients. All patients received both imaging modalities by 2 experienced (> 5 years experience) radiologists (nMRI) and four experienced (> 5 years experience) nuclear medicine physicians (68 Ga-PSMA-PET/CT). The standard imaging protocol within the hospital was used including patient and physician safety measures. Similarly for Pelvic Lymphnode dissection (PLND), the standard surgical protocol was used within the hospital with its patient and physician safety measures. Pelvic Lymphnode dissection was performed by an experienced surgeon (> 20 years) with the outcome of the nMRI and 68 Ga-PSMA-PET/CT imaging procedures. If suspicious lymphnodes on pre-operative imaging were also visible on postoperative MRI (six weeks after PLND) these were considered as not removed by PNLD. Positive LNs on preoperative nMRI and/or 68 Ga-PSMA-PET/CT were re-identified on postoperative MRI based on location, size and shape. The protocol was approved by the local institution review boards (NL55589.091.16).

Background therapy:

Extended lymph node dissection (ePLND) is the current reference-standard for nodal (N)-staging and should be performed in men with prostate cancer (PCa) and >5% risk of lymph node metastases (LNMs) according to the European Association of Urology (EAU) guidelines.

Evidence for comparator:

Conventional imaging techniques such as CT and MRI rely on lymph node (LN) size and morphology and therefore are of limited value. Two new molecular imaging techniques have demonstrated their ability to detect small LNMetastases (LNMs), combined with high specificity. These are nano-(n)MRI, which uses ultra-small iron oxide particles as contrast agent (ferumoxtran-10, Ferrotran®, SPL-Medical, Nijmegen, The Netherlands) and 68Ga PSMA-HBED-CC PET/CT (PSMA-PET/CT). With nMRI, very small LNMs can be detected with high sensitivity (91%). PSMA-PET/CT uses radio-labelled tracers that target the PSMA receptors which are overexpressed in prostate cancer cells. This enables total-body body imaging of LNMs and other metastases. Both techniques have the potential to improve N-staging and could be valuable tools to complement PLND. However, validation studies using PLND as a reference-standard are scarce and show high differences in sensitivity and specificity. Most studies are limited by the abscence of postoperative imaging to verify whether LNMs are removed. They also lack detailed histological validation on a node-by-node or regional basis and follow-up. Nevertheless, initial retrospective comparison of PSMA-PET/CT and nMRI has shown that both are able to identify small suspicious LNs in all anatomical regions of the pelvis, with nMRI detecting more and smaller suspicious LNs. However, a prospective validation study is needed to compare the diagnostic performance of PSMA-PET/CT and nMRI.

Actual start date of recruitment	01 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	22
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Forty-two men with newly diagnosed PCa and an estimated risk of metastatic LNs exceeding 5%, based on the Memorial Sloan Kettering Cancer Center nomogram (https://www.mskcc.org/nomograms/prostate/pre_op), were included in the study. These men underwent a nMRI and a 68Ga PSMA-HBED-CC PET/CT (PSMA-PET/CT) scan.

Pre-assignment

Screening details:

42 Patients were included after giving verbal and written informed consent.

Pre-assignment period milestones

Number of subjects started	42
Number of subjects completed	42

Period 1

Period 1 title	nano-MRI and PLND and PSMA-PET-CT (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No Blinding implementation details

Arms

Arm title	Nano-MRI and PSMA-PET-CT and PLND

Arm description:

Patients with nano-MRI, PSMA-PET/CT and PLND

Arm type	1-arm study
Investigational medicinal product name	ferumoxtran
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for parenteral use
Routes of administration	Intravenous use

Dosage and administration details:

(2.6 mg/kg body weight

Investigational medicinal product name	PSMA-PET-CT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 MBq/kg body weight

Number of subjects in period 1	Nano-MRI and PSMA-PET-CT and PLND
Started	42
Completed	42

Baseline characteristics

Reporting groups

Reporting group title	nano-MRI and PLND and PSMA-PET-CT

Reporting group description: -

Reporting group values	nano-MRI and PLND and PSMA-PET-CT	Total	
Number of subjects	42	42	
Age categorical			
The median age of 38 patients was 67 years with a range of 63-71 years.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	22	22	
From 65-84 years	20	20	
85 years and over	0	0	
Age continuous			
The median age in 38 patients was 67 with a range of 63-71 years.			
Units: years			
median	67		
full range (min-max)	63 to 71	-	
Gender categorical			
males			
Units: Subjects			
Female	0	0	
Male	42	42	

Subject analysis sets

Subject analysis set title	Per Protocol Analysis
Subject analysis set type	Per protocol

Subject analysis set description:

38 Patients received all study procedures and are included in the final analysis

Reporting group values	Per Protocol Analysis		
Number of subjects	38		
Age categorical			
The median age of 38 patients was 67 years with a range of 63-71 years.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	20		
From 65-84 years	18		
85 years and over	0		
Age continuous			
The median age in 38 patients was 67 with a range of 63-71 years.			
Units: years			
median	67		
full range (min-max)	63 to 71		
Gender categorical			
males			
Units: Subjects			
Female	0		
Male	38		

End points

End points reporting groups

Reporting group title	Nano-MRI and PSMA-PET-CT and PLND
Reporting group description: Patients with nano-MRI, PSMA-PET/CT and PLND	
Subject analysis set title	Per Protocol Analysis
Subject analysis set type	Per protocol
Subject analysis set description: 38 Patients received all study procedures and are included in the final analysis	

Primary: Correlation ePLND with postoperative MRI

End point title	Correlation ePLND with postoperative MRI[1]
End point description: On the postoperative MRI 60 of the 74 (81%) nMRI-positive LNs and 23 of the 29 (79%) PSMA-PET/CT-positive LNs were still present. On a per-patient level, this was 17 of the 29 (59%) men for nMRI and 13 of the 19 (68%) for PSMA-PET/CT. No LNs with positive findings on imaging were extracted from the para-aortic, common iliac, presacral, and para-rectal regions. The largest number of LNs with suspected positive findings on imaging were removed from the external iliac region (48%).	
End point type	Primary
End point timeframe: 6 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Simple comparative statistics was used.

End point values	Per Protocol Analysis			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: 38	38			

Statistical analyses

No statistical analyses for this end point

Primary: Histopathologic results

End point title	Histopathologic results[2]
End point description: Among the 38 men analyzed, 13 (34%) had histopathological confirmed metastatic LN. Of the 915 resected LNs, 22 (2.4%) contained metastasis with a median size of 3 mm (range 2-18 mm). Fifteen (68%) of these metastatic LNs were smaller than 4 mm. Nano-MRI identified 13 out of 22 lymph nodes as true positives (TP), 1 as false positive (FP), and missed 9 as false negatives (FN; Table 2). Among the 13 correctly identified LNs, 5 were larger than 5mm, 6 ranged from 2-5mm, and 2 were smaller than 2mm. The PSMA-PET/CT examination revealed 6 out of 22 (27%) true positive LNs, 1 out of 22 (4.5%) false positive LN, and 16 out of 22 (73%) false negative LNs. Among these, 6 out of 22 LNs were metastatic, with 4 being larger than 5 mm, 1 between 2 to 5 mm, and 1 smaller than 2 mm. At the patient level, nMRI identified 1 out of 13 (8%) false negative patients, while PSMA-PET/CT identified 7 out of 13 (54%) false negative patients.	
End point type	Primary

End point timeframe:

4 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Simple comparative statistics was used.

End point values	Per Protocol Analysis			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: 38	38			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: from 2016-2017	
Adverse event reporting additional description: No adverse events	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	LAREB
Dictionary version	1

Frequency threshold for reporting non-serious adverse events: 0.1 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: To our knowledge there were no adverse events reported

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A major limitation of the study is the presence of a high number of non-removed, preoperatively suspected LNs on imaging, which hinders the validation of the diagnostic accuracy of both imaging methods using histopathology as the reference standard.

Notes: