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PET-CT in the sub-arctic region of Norway

A follow up-study

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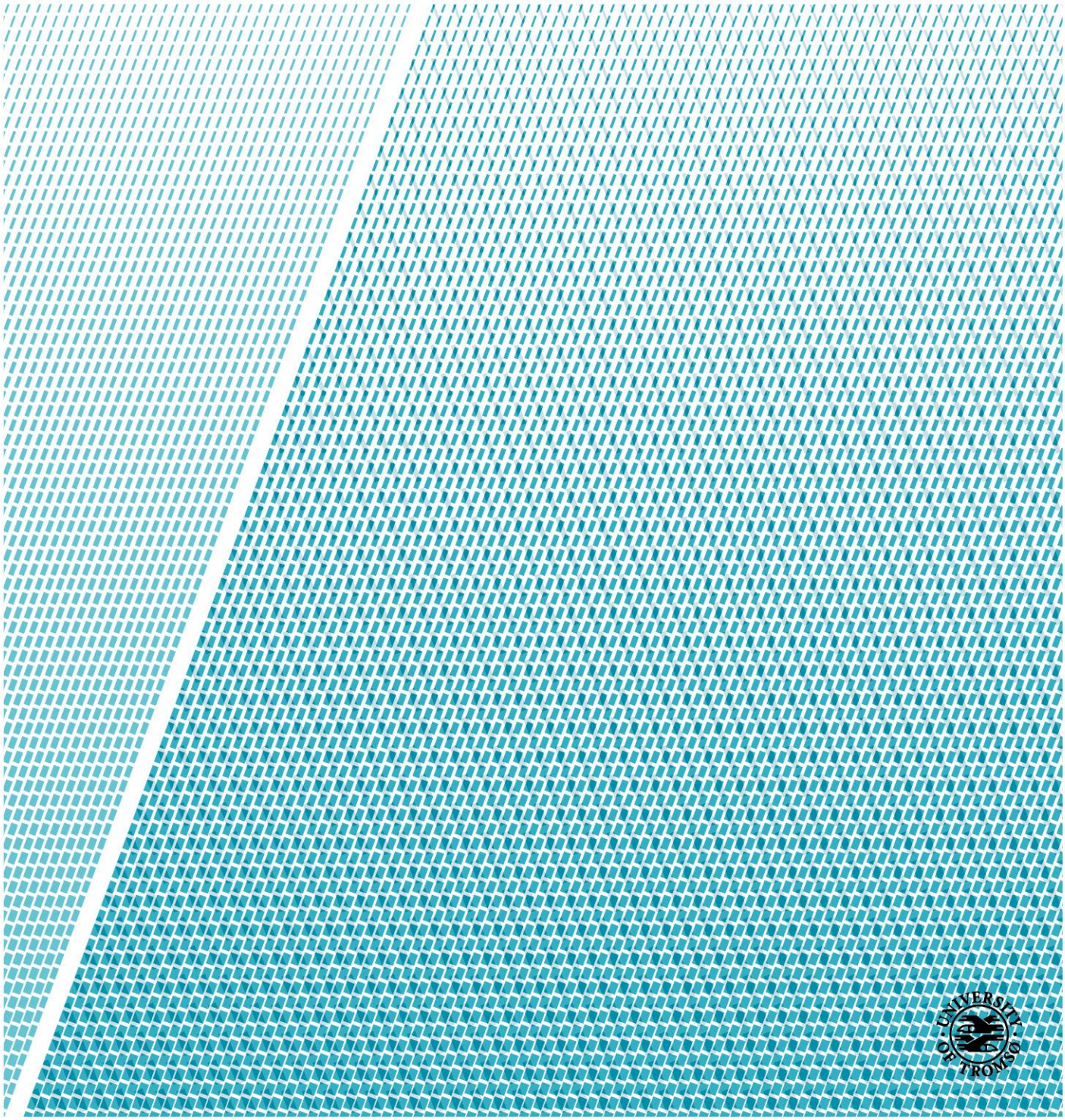

Acknowledgment

The goal of this study is to monitor the massive development that there has been in nuclear medicine in Northern Norway during the last 7 years with the focus on the patient population. This is to make sure that the population that has access to the PET/CT-scanner in Tromsø is representative of the population in Northern Norway, with no subgroup overlooked, and to get an overview of the patient population.

I first contacted Rune Sundset in the spring of 2015, after getting the contact information from Vegard Skogen, the head of the research education program in the medical education in Tromsø. The reason I contacted Rune Sundset, of the nuclear medical research group, is that I have always been interested in physics, and was curious about how nuclear physics was utilised in medicine. Rune suggested a follow up study to one carried out by Jan Norum a year earlier, and he also contacted Ursula Søndergaard, a medical physicist, to be my coadvisor. Thus, the project was born.

The project description was written in the fall of 2015, and the first data was extracted from the medical imaging program at UNN in the winter of 2016. Most of the work with the datasheet was done during the summer and fall of 2016, and only minor details remained when entering 2017. Most of the statistics and writing was done during winter and spring of 2017. The plan is for this study to eventually be published in an article form.

I want to thank my advisors for good guidance and co-operation with this thesis. This thesis would not be possible without their good insight in research methods and design. Especially I want to thank Ursula, who gave birth to her first-born during the last period of this thesis, but still managed to answer my questions and give good advices during this period. I wish them both the best of luck.

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1 Abstract

1.1 Purpose

It is challenging to provide equal access to advanced diagnostics in the sub-arctic region of Norway. The goal of providing a high quality to Positron Emission Tomography/Computer Tomography centre (PET/CT) is challenging due to vast distances and weather condition. This study is a follow-up study on a previous analysis done by Norum et al. to examine the availability of the PET/CT service in the University Hospital in Northern Norway (UNN), situated in the city of Tromsø.

1.2 Method

In 2016, the patient data from all PET/CT examinations in 2014 and 2015 was retrospectively analysed. The data was divided in subgroups based on gender, home address, county, age and diagnosis. Descriptive statistics was performed, and subgroups were compared using Pearson's Chi-Square test to detect and quantify any inequality in access to PET/CT examination.

1.3 Results

In 2014 and 2015 a total of 907 PET/CT scans were performed in 825 patients at the PET Imaging Centre in UNN, Tromsø, giving an average of 1,1 PET/CT examinations per patient. In 2015 there was an average of 1069 PET/CT scans per million in Northern Norway. Lung cancer (36,4%), lymphoma (18,0%), head and neck cancer (10,0%), and malignant melanoma (6,7%) were the most frequent diagnostic groups. The northernmost county, Finnmark, had more PET/CT scans than both Troms and Nordland (P=0,012) on average, but the distribution between counties varied with the diagnostic group. Nordland had more PET/CT scans in malignant melanoma patients than both Troms and Finnmark. The mean travelling distance to the PET centre were 406 km with range from 4,8 km to 939 km.

1.4 Conclusion

The difference in availability to PET/CT examination between counties in Northern Norway has decreased since 2010-2013, but there is still a difference present. Finnmark has on average more PET/CT examinations per head of population, while Nordland has more scans in

malignant melanoma patients. The difference in cancer incidence cannot explain this difference alone, and other factors may influence the distribution in access to PET/CT examination in Northern Norway.

2 Introduction

2.1 Medical imaging

Radiology as a medical field began with Wilhelm Röntgen's discovery of X-rays in 1895 while working with his cathode ray tube. For this he was awarded the Nobel Prize in Physics in 1901 (1). People soon began to realise the potential medical uses for the technology, and the first clinical X-ray image was done in 1896 (2). The further development of radiographic films and screens made x-ray imaging more popular during the 1920s (3).

Today, there are several modalities in medical imaging, each with their own advantages and disadvantages. The most common in use are

- X-ray (Projectional radiograph)
- X-ray Computed Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Ultrasound devices.

All these modalities have in common that they can examine the patient's anatomy and physical properties non-invasively (3).

2.2 Nuclear medicine

Nuclear medicine uses radioactive isotopes to do both medical imaging and therapeutics. This differs from radiological modalities in that nuclear imaging depend on molecular biology and physiological processes to generate pictures, where radiological modalities depend on physical properties of the chemical structures in the body to generate pictures, whether this is electron density (x-ray), echogenic properties (ultrasound) or proton density (MRI) (4).

Radioactive isotopes chemically bonded to a biologically active molecule (radiopharmaceutical) can in theory image all biological pathways in the body, depending on the radiopharmaceutical in use.

The most common modalities in nuclear imaging are (5):

- Scintigraphy
- Single photon emission computed tomography (SPECT)
- Positron emission tomography (PET)

These modalities are often combined with CT, or recently MRI, to make a hybrid scanner. This produces both good contrast from the nuclear medical image, and anatomical landmarks or, for instance, additional functional information from the other modality (6).

2.3 Positron emission tomography (PET)

A positron emission tomography scanner is in its simplest form a circular so-called “gamma camera” (a detector system sensitive to gamma radiation), like those used in scintigraphy, that reconstruct a 3D image in the same way a CT does. The main difference is that most CT have an x-ray tube to produce radiation to shine through the patient, and one image sensor in the opposite end; This does circular movements around the patient to make 2D slices of the patient. In a PET-scan the substance producing the radiation is inside the patient, and therefore it can have fixed sensors around the patient (fig. 1) (7).

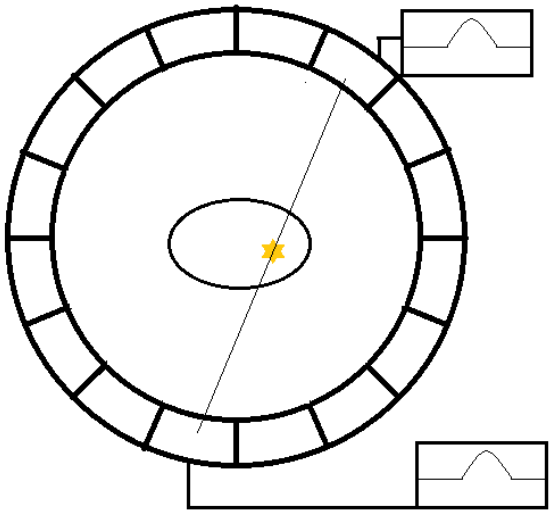

Figure 1 A simplified figure showing an annihilation occurring in a patient inside a PET scanner, producing two gamma photons which travels to two sensors, which will detect a spike in approximately the same time. Note: number of sensors is not to scale.

When a radiopharmaceutical, as the ones used for PET (see below in 2.6 Radiopharmaceuticals), produces two gamma photons travelling in opposite directions, two of the sensors in the sensor ring will detect a spike approximately at the same time (fig.1). Using the position of the two sensors, the computer can calculate a line where the photons must have come from. With several of these lines in multiple directions, you can make a 2D slice representation of the patient. By making several of these slices and joining them together, you get a 3D reconstruction of the patient (7).

Another technique in use in some PET-scanners is to look at the time difference between the two photons, and then calculate where on the line between the sensors the two photons must have occurred. This technique is called 'Time of Flight' (7).

PET-scanners provides good contrast in pictures, but poor anatomical resolution. Therefore, it is normal to have scanners with both a PET-detector ring and a CT-scanner or MRI-scanner in front. By using the exact position of the table on which the patient is lying, and the distance between the CT-scanner and the PET-scanner, one can overlap these two images, and get both a good contrast, and a good anatomical overview (7).

2.4 Clinical use of PET-CT

The role of PET as a diagnostic tool has been established in a wide variety of malignant and inflammatory diseases, both in initial staging and follow up (8). In clinic, the most common use of PET-CT is with the tracer 18F-fludeoxyglucose (FDG) (9). This is a glucose molecule marked with radioactive fluorine (18-F). This modified glucose molecule will enter glucose metabolism and become phosphorylated. The modified glucose molecule is prevented from being released from the cell, and therefore provides a good reflection of the distribution of primary glucose uptake. Cancerous and inflammatory cells have high glucose uptake, and thus, the use of FDG-PET/CT is useful in these clinical cases (5). FDG-PET/CT is used for accurately diagnosing, initial staging, response assessment, and follow-up in several cancers. FDG-PET is generally superior to CT scans alone (8). A meta-analysis found a sensitivity and specificity of 96,8% and 77,8% respectively with monomodal FDG-PET in diagnosing lung tumours, compared to 61% and 79% with CT alone (10). Inflammatory diseases where FDG-PET(-CT) is often used, are large vessel vasculitis, sarcoidosis, and infection with unknown focus (5).

With the development of new tracers, new ranges of applications emerge. This is useful in areas where FDG-PET has been of little value. The central nervous system (CNS) have a high baseline glucose metabolism, and with regular FDG-PET, the signal-to-baseline ratio is not sufficient to give good contrast between regular, neurological tissue and pathological processes in the same area (11). To overcome this, more specific tracers have been used for neurological diseases, like amyloid-β tracers in Alzheimer's disease (12).

Prostate cancer is also a diagnosis that is difficult to determine the extent of its invasion and metastasis with FDG-PET because of the urinary excretion of FDG. This produce more background noise in the pelvic area, and cause a bad signal-to-noise ratio (13). The European guidelines from European Association of Nuclear Medicine (EANM) recommends the use of a prostate-specific membrane antigen (PSMA) tagged with generator produced 68-Gallium (68-Ga) (14). There are several of these on the market, but they are collectively known as 68-Ga-PSMA (14).

2.5 Radioactive decay

Radioactive decay is when the nucleus of an unstable isotope decays to a lower energy state. When an unstable nucleus decays, a small portion of the mass will transform into energy, as described in Einstein's mass-energy relationship.

$E= mc^2$

E is energy, m is mass and c is the speed of light in vacuum. This energy is released as radiation in some form. Radiation can be divided into two main categories, electromagnetic radiation and particle radiation. Electromagnetic radiation is a form of energy that does not have mass or charge. This package of energy is called photon or light quanta. This radiation can behave both as waves and as particles, and have the velocity of light. Examples of electromagnetic radiation are gamma-rays, x-rays and visible light. Particle radiation is particles with mass, that can have charge, and that they are emitted when the nucleus decay. Their velocity is determined by the kinetic energy they receive in the decay (7).

There are several pathways by which a nucleus can decay, but this thesis will focus on the positron decay, since it is most relevant to the PET.

Positron decay occurs when a nuclide has a higher proton/neutron-ratio than the nearest stable nuclide. Another requirement is that the parent nuclide must have 1,022 MeV more mass-energy than the daughter nuclide. This is to satisfy the energy conservation law. In a positron decay a proton is converted to one neutron (n), one positron (β^+) and one neutrino (v) (7). The positron and the neutrino are ejected from the decaying nucleus in the process, sharing the kinetic energy between them, whereas the neutron is confined to the new nucleus.

$P \rightarrow n + \beta^+ + v$

A positron is the antiparticle of the electron, with a charge of +1, instead of the electrons -1 charge. In the presence of matter, the lifespan of a positron is extremely short. When travelling through a medium, the positron will only travel a short range before it loses its kinetic energy and meets an electron. When this happen, they will interact in a process called annihilation giving rise to two gamma photons which are emitted in opposite direction. These are the

gamma-rays we can detect in a PET-scan. Some examples of nuclides which mainly decay by positron emission are F-18, C-11, N-13 and O-15 (7).

2.6 Radiopharmaceuticals

A Radiopharmaceutical is a biologically active molecule that is coupled with a radioactive isotope. The biological molecule depends on the biological component or pathway one wants to study, such as an antibody, metabolic pathway or an amino acid. In theory, this can be every molecule in the body, but is limited to what type of isotope that can chemically bond with the chemical compound that is of an interest (4).

To make radiopharmaceuticals you first must make or extract the radioactive isotope. To do this you need a particle accelerator or a generator. The most common particle accelerator in use is the cyclotron. The principle of this is that it accelerates particles, for instance protons, in a spiral to make a particle beam. This beam hits a target with such force that it creates a nuclear reaction. By bombarding different targets, one can make different isotopes, also radioactive ones (4).

The second step is to chemically bind this isotope to the biologically active molecule that is of interest, for instance glucose or an amino acid. Some isotopes have such a short half-life that they must be channelled directly from the cyclotron, to the patient (7).

Because of its relatively long half-life of 110 minutes and its chemical avidity, F-18 is the most common isotope in use. It can bind to glucose to make FDG which is suitable to monitor glucose metabolism, for instance in cancer and inflammatory diseases (7). F-18 FDG has proven itself to have a high clinical value in a variety of clinical cases due to being able to target many different diseases.

Other isotopes in clinical use are nitrogen-13 and rubidium-82 in cardiac perfusion imaging (15), and nitrogen-13, carbon-11 (16), and copper-64 in neuroimaging (11). These isotopes are not in use in UNN, so their physical and pharmaceutical properties will not be further discussed in this thesis.

2.7 Pearson's Chi Square test

In this study, the subgroups within the patient data will be compared to each other using the Pearson's Chi Square test. Pearson's Chi Square test is a statistical test to evaluate if there is statistically significant difference between a group and an expected, theoretical distribution in a population. A null hypothesis is formulated, normally that there is no difference between the groups. Pearson's Chi Square test can be used to test whether the null hypothesis is correct or not. The equation is:

$$X^2 = \sum \frac{(O - E)^2}{E}$$

O is the observed number and E is the expected number. After finding the X^2 the degrees of freedom (dF) in the population needs to be determined. This means finding out how many variables are needed before the rest can be calculated. This is expressed by the equation below where N is the total number of observations.

$$dF = N - 1$$

When both X^2 and dF is found, standardized tables are used to determine the P-value of the test. The P-value determine if the difference between the group and the theoretical distribution in the general population is statistically significant to the required degree.

The Pearson's Chi Square test has some predetermined assumptions. The first assumption is that the data of interest is a true random sampling from a fixed distribution in a population. The second assumption is that the sample is of sufficient size to truly reveal the difference. If not, a false negative error can occur. The third assumption is that all cells in the table has sufficiently large numbers. A rule of thumb is that it is necessary to have 5 or more in all cells in a 2x2 table, and 5 or more in 80% of the cells in a larger table. If this is not met, the Yate's correlation can be used. The last assumption is that the observations are independent of each other (17).

2.8 Background

The idea of launching PET service in Norway was first discussed in 2000 (3). The decision to create a PET centre in Norway was taken in 2004 (18), and the first PET centre was built in Oslo in 2005. In 2009, the Norwegian Knowledge Centre (Kunnskapssenteret) calculated that the number of PET/CT scanners needed in Norway was between 4 and 14, depending on whether PET/CT should be implemented in radiotherapy planning or not (19).

Following this introduction of PET/CT service in Norway, it became clear that there was an uneven distribution of availability that was dropping with the distance from the centre, especially in Northern Norway (20). To counteract this trend, the University Hospital in Northern Norway initiated a process to establish a PET/CT scanner in Tromsø.

The PET/CT scanner in Tromsø was established in May 2010. The scanner was supposed to serve Northern Norway, and its three counties, Nordland, Troms and Finnmark. The city of Tromsø is located approximately in the centre of this region with 900 km to the Russian border in the east, and 800 km to the southern border of Nordland. Due to this vast area, and a population of only 464 000 inhabitants (2010), establishing a PET/CT scanner here would demand a cost-effective solution.

At first, FDG was obtained through MAP Medical Technologies in Helsinki, Finland. Initially a private company served Tromsø, along other hospitals in Scandinavia and Estonia, with a mobile PET/CT scanner placed in a semi-trailer. This solution was replaced in October 2011 by a stationary scanner in Tromsø, and in November 2012 a permanent, self-owned PET/CT scanner was established (20). Since 2015 the FDG has been produced in Oslo due to a new tender process.

In 2015, a study that looked at the availability to PET/CT in the different counties, Nordland, Troms and Finnmark was published (20). This study observed that the availability decreased with longer travel distance to the PET/CT-scanner. The difference was most prominent for the southern county in Northern Norway, Nordland. This study reveals a need to make PET/CT examination more available (20).

After this study, the section of nuclear medicine (now Department of PET Imaging Centre), UNN, did take some measures to ensure that patient from Nordland got equal access to PET/CT as the rest of the region. The measures taken were.

- 2015: The multidisciplinary team at Nordland Hospital, Bodø got one slot reserved each week (20).
- Increased capacity of the scanner: In 2016, the number of days with scanning per month increased from 4 to 5, and in 2017 it increased to 8 days a month (personal communication dr. Rune Sundset, UNN). Since these measures was taken in 2016 and 2017, they have not affected the data set in this study.

2.9 Aim of Study

This is a follow-up study of Norum 2015 (20). The aim of this study is to investigate whether the difference in availability to PET/CT service between the three northernmost counties in Norway, which was observed between 2010 and 2013 continued in 2014 and 2015, or if there is an improvement in availability to the PET-service at UNN, Tromsø.

This study does not look at the clinical outcome of the patient, and is not meant to verify the clinical value of FDG-PET/CT. This study does not evaluate the quality of the referral practice within the different hospitals and health trust in the region.

3 Methode

3.1 Data included and analysis tools

The population in this study consists of all PET-CT scans at UNN in the period 2014-2015. The data was retrospectively extracted from the medical imaging information system (TRIS), and then manually checked against the written documents at the PET Imaging Centre. The data extracted was name, personal ID number, date of examination, residence and clinical problem.

To make the final dataset, Microsoft Excel 2016 was used, and IBM SPSS 24 was used for statistical analysis and descriptive analysis. By using the personal identification number, age and sex was obtained. By reading the clinical problem, all patients were categorised using the same standard diagnostic categories as the previous study (20). However, in the dataset received from 2010-2013 thyroid cancer had been categorized as "head and neck cancer". To avoid disparities, this definition was also used in this study.

With the registered residence, the population was divided into three categories based on their county, and the driving distance from residence to UNN, Tromsø was calculated using the postal code and Google Maps (www.maps.google.com). The number of inhabitants in the three counties (Nordland, Troms and Finnmark) was calculated using data from Statistics Norway (www.ssb.no).

The three patient groups were compared to each other with descriptive statistics. The rate of number of PET/CT examinations per capita was calculated, and then compared with a regional average to create a ratio number between PET scans in county and in the region. This number were compared with the same numbers from Norum 2015 (20) in the period 2010-2013. Pearson's Chi Square test were used to verify a significant difference between Nordland, Troms and Finnmark in the period of 2014-2015.

Due to the switch from TRIS information system to SECTRA information system, the home address from the last 183 patients in 2015 was not included in the statistics. Unfortunately, this error was not discovered in time to be corrected in this thesis, but will be included, together with the 2016 data in the planned publication. The implication of this in the current study is examined in the discussion.

3.2 Authorisation

The study was carried out as a quality of care analysis and consequently no ethical committee or Data Inspectorate approval was necessary. Similarly, no approval from the Regional Committees for Medical and Health Research Ethics (REK) or from the Norwegian Social Science Data Services (NSD) was necessary.

4 Results

The number of PET/CT scans performed per year at UNN Tromsø has increased since the start in 2010 (figure 3). The total number of PET/CT scans was 907 in the period 2014-2015 in 825 individual patients. This gives an average of 1,1 examinations per patient. There is more than a fourfold increase in scans per year from 2010 to 2015.

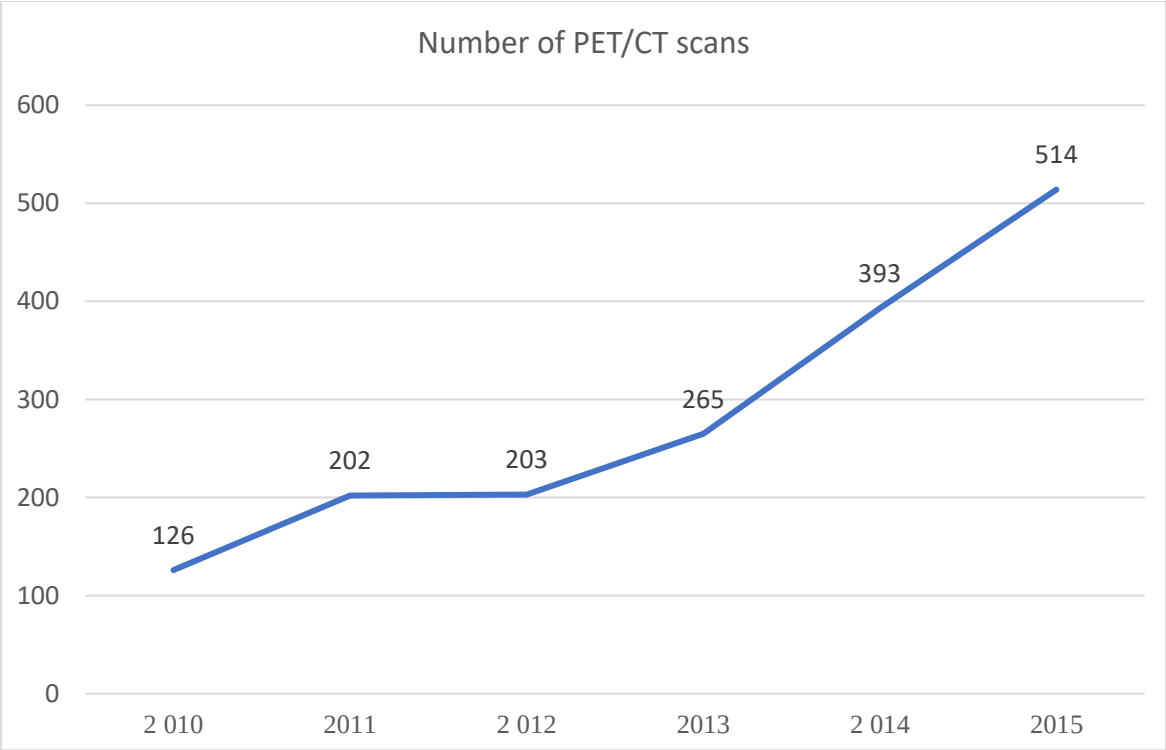

Figure 2 Total number of PET/CT scans performed at UNN, Tromsø per year from 2010 to 2015.

Table 1 *An overview of PET/CT examinations. Total, sex, county and diagnosis are shown in total (n) and percentage (%) (2014-2015).*

		Examinations	
Variables		PET/CT	%
Total		907	100
Sex	Male	551	61
	Female	356	39
County	Nordland	348	46
	Troms	268	30
	Finnmark	145	16
Diagnosis	Lung cancer	330	36,4
	Lymhpoma	163	18,0
	Head and neck cancer	91	10,0
	Malignant melanoma	61	6,7
	Colorectal cancer	55	6,1
	Gynaecological cancer	34	3,7
	Urogenital cancer	30	3,3
	Upper GI-cancer	22	2,4
	Breast cancer	5	0,6
	Cancer, unknown origin	26	2,9
	Other cancers	30	3,3
	Inflammatory disease	46	5,1
	Sarcoidosis	4	0,4
	Others	5	0,6

There was no significant difference between age distribution between genders. The mean age among males was 61, and 59 years among females. Standard deviation was 15,4 and 15,5 respectively. As seen here, there is a discrepancy between the total number of PET/CT scans (907) and the combined number of PET/CT from the three counties (760) (table 1). This is

due to the change from TRIS image information system to SECTRA that led to a deletion of the home city number for the patient that had a PET/CT scan in November and December in 2015, and affected 147 patients. To not distort the statistics, these 147 patients were left out in the statistics below where the counties are compared.

Table 2 The ratio of PET/CT exams/population in total and in each county. The figure of all three northern counties was set to one in each diagnostic group. (For example: All exams: 760/479 000 inhabitants = 0,16% =1.00. The same numbers for the period 2010-2013 were gathered from Norum 2015 (20) for comparison.

	Nordland		Troms		Finnmark	
	2010-2013	2014-2015	2010-2013	2014-2015	2010-2013	2014-2015
Lung cancer	0,57	0,89	1,34	0,96	1,66	1,4
Lymphoma	0,67	0,89	1,62	1,11	0,74	1,1
Malignant melanoma	0,99	1,16	1,02	0,89	0,99	0,72
All examns	0,71	0,91	1,32	1,04	1,26	1,2

The general distribution of PET/CT use is more evenly distributed in the period of 2014-2015 compared with the period of 2010-2013, but in some diagnostic groups, the discrepancy is higher than the average. The group with the greatest difference was the lung cancer group, where Finnmark had 57% more PET/CT scans than Nordland. As was also found in the previous analysis Nordland is lowest in all groups, except for malignant melanoma, where Nordland had a higher PET/CT use. The other diagnostic groups were not compared between the counties because of small numbers of patients (table 2).

The mean traveling distance by car was 406 km (std.dev 271 km). The range was from 4,8 km (Tromsø) to 939 km (Sømna in Southern Nordland).

The incidence rate between Nordland, Troms and Finnmark in lung cancer (all types) and malignant melanoma. Finnmark has a considerable higher lung cancer incidence than both Nordland and Troms, and there is a gender difference also.

In malignant melanoma Troms has a higher incidence rate than both Nordland and Finnmark, and Finnmark has lower incidence rate than Nordland.

Table 3 Age standardized lung cancer incidence per 100 000 capita in Nordland, Troms and finnmark, as well as the national average (21)

	Male	Female	Average
Nordland	77,9	50,1	64
Troms	81,3	49,8	65,55
Finnmark	97,7	65,9	81,8
Norway	75,8	52,8	64,3

Table 4 Annual average 2011-2015. Age-standardized incidence rates per 100 000 inhabitants of melanoma of the skin in Nordland, Troms and Finnmark, as well as the national average (21).

	Male	Female	Average
Nordland	22,2	20,8	21,5
Troms	28,3	23,3	25,8
Finnmark	15,5	16,4	16
Norway	39,5	35,5	37,5

5 Discussion

In this study, it has been documented that the number of PET/CT scans per million inhabitants in Northern Norway has increased from 270 in 2010 to 1069 in 2015. In 2012 the European average was 1200 examinations per million inhabitants (9). Norway had a national average of 1500 PET scans per million inhabitants in 2014 (9). Thus, Northern Norway is below both European and Norwegian average. In comparison, Denmark had an average of 4900 examinations per million inhabitants in 2011 (9). The number of PET scans per million to cover all indications, was calculated to be 2026,5 scans/million by Bedford and Maisey in 2004 (22). Based on the rapid increase in number of PET/CT scans, and the fact that UNN has doubled their capacity from 2015 to 2017, it is reasonable to hope that the PET incidence in Northern Norway will reach European and Norwegian standards within few years. To control this, a new follow up study with 2016 and 2017 data needs to be conducted.

The significant increase in number of PET/CT scans in Northern Norway can be seen all over Norway (9). The total number of PET scans in Norway has increased from 80 in 2005 to 7525 in 2014 (9). In the western part of Norway, Haukeland University Hospital opened its PET service in 2009 and have had an increase from 293 in 2009 to 1616 in 2014 (9). This indicates that when a service is opened, a period of even increase is seen the first years. At the same time, the widespread use of PET/CT has increased in Norway. It is natural that when a service is opened, the demand will increase when the service is implemented in more guidelines in the future.

In Norum's study (20) Nordland (0,10%) had half the number of PET/CT scans per head of population when compared to Troms (0,20%) and Finnmark (0,19%). When compared to the regional average, the values were 0,71, 1,32 and 1,26 respectively (table 2). In this dataset, the same values were 0,91, 1,04 and 1,21 (table 2), which has far less variation between the counties. This shows a significant reduction in disparity between counties, but still, there is a general lower PET/CT use in Nordland, except in malignant melanoma, where the opposite is observed.

One reason for this disparity could be due to a "leakage" of patient from Nordland to other PET-centres in Norway. A frequently used centre is the private PET/CT scanner at Aleris in Oslo. Upon request, they reported that there were 78 PET/CT scans referred from a hospital within Northern Norway in 2015. This is 13% of all PET/CT examinations in northern Norway. Aleris also stated that ⅔ of the examinations was performed during the second half of 2015. This means that they have had an increase during 2015, and therefore one cannot assume that there has been an even percentage over time of patient from Northern Norway, and that this number has been lower in 2014 and first half of 2015. Since all these are within the same health trust, the data received from Aleris did not distinguish between the different hospitals or counties. Assuming a 13% percent referral rate, this could potentially shift the observed distribution between counties. Another explanation of this "leakage" is that the patient groups which is referred to other PET centres is referred because of clinical cases which UNN, Tromsø do not have PET/CT protocols for. This explanation would mean a more evenly distribution between counties than if one specific hospital referred more patient to other PET centres. To investigate this, a better method for controlling external use of PET/CT would have to be implemented.

Lung cancer was the most common indication among the PET/CT patients, accounting for 36,4 % of all patients (table 1). This means that differences in the lung cancer group can affect the general distribution in the PET/CT population to a high degree Finnmark has a 22% higher incidence of lung cancer than Nordland (table 3) (21), but had 36,5% more PET/CT scans in the lung cancer group. This implies that a difference in lung cancer incidence cannot explain all the difference in PET/CT use. The same was observed between Troms and Finnmark. Overall, Finnmark had a higher use of PET/CT per lung cancer incidence than both Troms and Finnmark, suggesting that there are other factors which affects the access to PET/CT examination in lung cancer patients. When all lung cancer patients were excluded, the difference between Troms and Finnmark evened out, while Nordland is still 18% below both Troms and Finnmark. A plausible reason for an increased lung cancer incidence in Finnmark is the historical smoking habits. Finnmark is still the county with the highest prevalence of daily smokers, and the difference is highest in the younger groups (23).

The role of PET/CT in malignant melanoma has been discussed (24). In stage I and II cancer, PET/CT has a high false positive rate, and the current consensus is that PET/CT adds little additional information in these patients (24). However, PET/CT is widely used in stage III and IV cancer. A retrospective study found that PET/CT had a sensitivity of 98,7% in patient with malignant melanoma, and recommended use in N and M staging (25). PET/CT is considered the gold standard in evaluation of additional, unsuspected lesion in patients with known malignant melanoma stage IV. In this study, malignant melanoma was the only cancer subgroup where Nordland had a higher use of PET/CT than Troms and Finnmark. Nordland was 30% above Troms and 61% above Finnmark in use of PET/CT. In Norum's study (20), it was found that malignant melanoma had an even distribution, in contrast with the other subgroups, where there was a big discrepancy. The strong cooperation between the plastic surgery department in the hospitals in Bodø and Tromsø was suggested to be one of the reasons for this. However, this does not explain a discrepancy of 60% between Finnmark and Nordland. Finnmark has some lower melanoma incidence rates (table 4), but Troms has the highest incidence in both genders, and should therefore be expected to have a higher PET/CT incidence in this patient group. Also, the difference in cancer incidence between Nordland and Finnmark is only 30%, and therefore potentially only accounts for half of the difference. Another factor that could contribute to this is the number surgeons from Tromsø that work in Bodø, or other reference differences between the hospital. This should however not be expected since the same surgeons work in both places.

One of the strength of this study, was the high number of patients included. All patient that had a PET/CT scan during the period was included, and therefore minimizing the risk of selection bias and promoting generalisation. One of the weaknesses with this study was that a portion of the patients in the population did not get registered with their home address. However, since this error happened in a point in time for all hospitals, the risk of bias is much smaller than if the error happened with a single hospital, or a single patient group, and the only implication is that there was a smaller patient number than originally planned. This error was not discovered in time to improve before the due date for this thesis, since it would have to been corrected manually in the patient data program (DIPS).

The future of PET examination in Northern Norway is looking bright. The PET imaging centre in UNN, Tromsø is nearing completion. Here, an inhouse cyclotron will make new

radiopharmaceuticals available and widen the research potential. A new PET/CT and a new PET/MR will further increase the capacity of the PET imaging centre. This, alongside a PET/CT stationed in Nordland Hospital, Bodø will further increase capacity and make PET/CT more available for the population within Nordland.

6 Conclusion

The disparity in availability to PET/CT service in Northern Norway has decreased since 2010-2013, but there is still a difference between the three counties. This was true for all diagnostic groups, except for malignant melanoma, where the disparity had increased. Overall, Finnmark has a higher use of PET/CT than both Nordland and Troms, and difference in cancer incidence cannot explain all the difference. This suggest that other factors affect the access to PET/CT availability in the northern parts of Norway.

7 References

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Kunnskapsevaluering

Referanse: Ruers, T. J., Wiering, B., van der Sijp, J. R., Roumen, R. M., de Jong, K. P., Comans, E. F., ... & Oyen, W. J. (2009). Improved selection of patients for hepatic surgery of colorectal liver metastases with 18F-FDG PET: a randomized study. *Journal of Nuclear Medicine*, *50*(7), 1036-1041.		**GRADE 4** Dokumentasjon **Ib** Anbefaling **A**	
Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer**
Undersøke om 18F-FDG-PET har nytteverdi i utredningen av colorectale levermetastaser for å avgjøre om de er operable. Første randomiserte studie om temaet **Konklusjon** **18-F-FDG-PET kan redusere antall resultatløse reseksjoner med 38%, og har potensiale for ennå større reduksjon hvis funnene blir tatt mer hensyn til, og når man nå har fått multimodale PET-skannere (PET/CT og PET/MR)** **Land** **Nederland** **År data innsamling** **Mai 2002-februar 2006**	**Randomisert kontrollert studie** **Studiet ble designet som en multisenter, randomisert kontrollert studie. Studiet ble designet for å oppdage en 15% reduksjon, og man trengte derfor 75 pasienter i hver gruppe.** **Kontrollgruppen ble satt opp til operasjon uten videre diagnostikk etter inklusjonskriteriene ble bekreftet, mens casegruppen ble satt opp til 18F-FDG-PET innen to uker (1-5).** **Endepunkt ble definert som «resultatløs lapratomi» hvis «resultatløst» ble definert som kirurgi som ikke resulterte i komplett remisjon i oppfølgingsperioden på 3 år. To andre endepunkter var overlevelse og sykdomsfri overlevelse.** **Inklusjonskriterier var pasienter med tidligere colorektal cancer som ble operert med fri reseksjonsrand, som hadde fått påvist levermetastaser (og maks to lungemetastaser) med konvensjonell CT-diagnostikk.** **Eksklusjonskriterier var følgende: Tidligere andre maligniteter som ikke hadde vært sykdomsfri i minst 10 år (unntatt in-situ carcinoma i cervix og nonmelanoma hudkreft), tegn til leversvikt, aktiv infeksjon og dårlig regulert diabetes mellitus.** **Gruppene ble sammenlignet med Fisher exact og T-test for kvantitative målinger. Overlevelse og sykdomsfri overlevese ble målt med Kaplan-Meier.**	**Fem pasienter i casegruppen fikk kansellert operasjonen sin. Tre pga ekstrahepatisk metastaser og to pga (korrekt) analyse som benign sykdom. Det betyr at 70 personer i casegruppen ble operert. Totalt fikk 45% av kontrollgruppen tilbakefall, mens kun 28% fikk det i casegruppen. Det gir en relativ risikoreduskjon på 38%, som gir NNT på 6 PET-skanninger for å spare en unødvendig lapratomi.** **Det var ikke signifikant forskjell i verken overlevelse eller sykdomsfri overlevelse (P=0,378 og P= 0,194)** **18F-FDG-PET forutså negativt utfall av lapratomi i 15 pasienter, men funnene ble ignorert i 10 av disse av teamet som avgjorde operabilitet. Alle disse 10 fikk tilbakefall av sykdom.**	**En av styrkene til denne studier var det randomiserte designet. Det har kun blitt gjort nonrandomiserte studier tidligere på dette feltet. Multisenterdesignet øker også generalisering og minsker sjansen for bias.** **Svakhetene med studiet er at spørsmålet om operabilitet ble gjort fra case til case og at det i 10 tilfeller viste seg at PET-funnene ble ignorer. Dette fører til en maskering av det virkelige potensialet til PET-undersøkelsen, og differansen mellom observert forskjell og faktisk forskjell blir i større grad opp til retrospektive analyser. En annen av svakthetene til studien er at ved publikasjonsdato var allerede mange av retningslinjene for operabilitet endret, man hadde fått perioperativ, adjuvant kjemoterapi inn i retningslinjene, og multimodale PET-skannere hadde allerede gjort innpass i klinikken. Dette er med på å gjøre studien mindre aktuell klinisk, men ikke i slik grad at den ikke er relevant.** **Funnene stemmer overens med to metaanalyser som ble gjort av alle nonrandomiserte studiene som var gjort på tidspunktet**

Referanse: A, Pfeifer, U, Knigge, J, Mortensen . Clinical PET of Neuroendocrine Tumors Using 64Cu-DOTATATE: First-in-Humans Study. J Nucl Med. 2012;53:1207-1215. Published online: July 10, 2012.	GRADE	2
	Dokumentasjon	IIa
	Anbefaling	B

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer
Validere klinisk bruk av 64Cu-DOTATATE i nevroendokrine tumorer (NET) mtp bildekvalitet og biodistribusjon, samt sammenligne med dagens regime med SPECT/CT med 111In-DTPA-octreotide **Konklusjon** **64Cu-DOTATATE egner seg godt til avbilding av NET og gir bedre bildekvalitet, samt lavere strålebelastning på pasienter sammenlignet med 111In-DTPA-octreotide** **Land** **Danmark** **År data innsamling** **Fra november 2009 til januar 2010**	**Tverrsnittsstudie (diagnostisk testvurdering)** **14 pasienter med histopatologisk bekreftet NET mellom nov. 2009 og jan 2010 som ble henvist til konvensjonell somatostatin receptor imaging (SRI). Ingen randomisering eller kontrollgruppe** **Inklusjons-/eksklusjonskrit.** - **Histopat. Bekreftet NET** - **Henvist SRI** **Datagrunnalget** - **14 pasienter med NET** - **Scan etter 1 time (n=14), 3 timer (n=12) og 24 timer (n=5)** **Utfall (outcome) validering** **(for eks. diagnose)** - **Antall Volumes of interest (VOI)** - **Bildekvalitet** - **PET/CT- og SPECT/CT-bildene ble analysert av to team med to erfarne nukleærmedisinere, som ble blindet for hverandres konklusjoner.** - **Som kontrollgruppe ble kun CT-bildene avlest av en erfaren radiolog** - **For å validere resultatene ble det gjort kontroll ved 18 mnd ved CT og konvensjonell SRI** **Statistiske metoder** **Gjennomsnitlig doseberegninger i de forskjellige organene ble gjort ved gjennomsnitt av 5 pasienter med standardavvik.** **Antall lesjoner ble summert for hver modalitet.**	**Hovedfunn:** **- 64Cu-DOTATATE PET/CT viste seg å finne flere vervifiserte lesjonen enn 111In-DTPA-octreotide SPECT/CT. Henholdsvis 219 lesjoner mot 115 lesjoner. Alle lesjonene som ble funnet på SPECT/CT ble også funnet på PET/CT. I 5 pasienter ble det funnet lesjoner i organer som ikke var positive på SPECT, noe som er ekstra interessant da det forandre behandlingsgrunnlaget.** **Bifunn:** - **PET/CT ga betydelig bedre bildekvalitet og oppløsning enn SPECT/CT.** - **I bakgrunn av de 5 pasientene som ble målt doseberegning på, fant man ut at 111In-DTPA-octreotide SPECT/CT ga betydelig høyere dosebelastning enn 64Cu-DOTATATE PET/CT. Henholdsvis 12 mSv og 6 mSv** - **Bildene kan tas 1 time etter injeksjon, og pga middels lang halveringstid (12,701 min) kan 64Cu-DOTATATE produseres sentralt og distribueres til andre fasiliteter i området.**	**Det er betydelig bedre bilder ved bruk av 64Cu-DOTATATE PET/CT enn 111In-DTPA-octreotide. Det har også blitt påvist at det blir oppdaget flere lesjoner ved PET/CT enn SPECT/CT i de samme pasientene.** **PET/CT gir lavere stråledose. Forfatterne mener at til tross for det lave antallet pasienter det ble gjort stråledoseanalyse på, er forskjellen så stor at det er et sterkt resultat. Resultatet styrkes av at det ble gjort på de samme pasientene for både PET og SPECT.** **Man har sett samme resultat for andre 64-Cu-merkede somatostatinanaloger hvor det er sammenlignet med 111In-DTPA-octreotide SPECT/CT.** **Forfatterne diskuterer om forbedringen er grunnet isoopen(64Cu) eller analogen (DOTATATE). Man har sett at 68Ga-DOTATATE og 68Ga-DOTATOC også gjør det bedre enn 111In-DTPA-octreotide, slik at man må sammenligne 64Cu og 68Ga direkte for å avgjøre dette.**

Referanse:Tlili, G., Amroui, S., Mesguich, C., Rivière, A., Bordachar, P., Hindié, E., & Bordenave, L. (2015). High performances of 18F-fluorodeoxyglucose PET-CT in cardiac implantable device infections: A study of 40 patients. Journal of Nuclear Cardiology, 22(4), 787-798.	**GRADE 2**		
	Dokumentasjon	**IIa**	
	Anbefaling	**B**	
Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer**
Validere diagnostisk verdi av 18-F-FDG-PET/CT i diagnostiskk av infeksjon i Cardiovascular implantable electronic devices (CIED) **Konklusjon** **18-F-FDG-PET/CT er nyttig i diagnostikken av infeksjon i CIED. De lovende resultatene i denne studien må valideres i en større multisenterstudie.** **Land** Frankrike **År data innsamling** 2009-2011	**Tverrsnittsstudie** **Gruppe 1: personer med Cardiovascular implantable electronic devices (CIED) med mistanke om infeksjon** **Gruppe 2: Personer med CIED uten mistanke om infeksjon, men som ble henvist til PET-CT for onkologiske grunner.** **Inklusjons-/eksklusjonskrit.** **Fått implantert CIED mellom 2009 og 2011. Hatt den implantert i minimum 2 mnd.** **Datagrunnalget** **40 i casegruppe, 40 i kontrollgruppe** **Utfall (outcome) validering** **(for eks. diagnose)** **Bildene ble undersøkt av to nukleærmedisinere som var blindet for andre kliniske opplysninger. Hvis de var uenige, møtes de for å enes om en konsensus** **Gullstandard ble i denne testen satt som positiv dyrkning ved eksplantasjon, eller klinisk oppfølging i 1 år mtp infeksjon** **Statistiske metoder** **Det ble beregnet sensistivitet, spesifisitet, NPV og PPV**	**Hovedfunn:** **Sensitivitet 83%, spesifisitet 95%, NPV 88% og PPV 94%. Alle i kontrollgruppen var negativ.**	**Styrke: Sterke resultater, spesielt høy spesisfisitet.** **Svakhet: Retrospektiv studie, samt vanskeligheter med å detektere forhøyet FDG-opptak grunnet høy bakgrunnsopptak i myokard. Dette skyltes manglende dietregulering forut for undersøkelsen** **Hva diskutere forfatterne ?** **Forfatterne diskuterer om FDG-PET/CT skal implementeres i utredningsalgoritmen. Spesielt pga den høye spesifisiteten mener de at det burde implementeres.** **Annen litteratur som styrker funnene?** **PET/CT brukes mer og mer på forskjellige typer infeksjoner, og tar i større grad over for leukocyttscintigrafi. Det er andre studier som har undersøkt mtp endokarditt. Chen, W., Kim, J., Molchanova-Cook, O.P. et al. Curr Cardiol Rep (2014) 16: 459. doi:10.1007/s11886-013-0459-y** **Og en studie har sett på om man skal gjøre undersøkelsen 1 time eller 3 timer etter injeksjon av F18-FDG** **Leccisotti, L., Perna, F., Lago, M. et al. J. Nucl. Cardiol. (2014) 21: 622. doi:10.1007/s12350-014-9896-2**

Referanse: Huellner, M. W., de Galiza Barbosa, F., Husmann, L., Pietsch, C. M., Mader, C. E., Burger, I. A., ... & Veit-Haibach, P. (2016). TNM Staging of Non–Small Cell Lung Cancer: Comparison of PET/MR and PET/CT. Journal of Nuclear Medicine, 57(1), 21-26.		**GRADE**	**2**
		Dokumentasjon	IIa
		Anbefaling	B

Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer**
Formålet med studien er å validere bruk av PET/MR ved NSCLC, og sammenligne med PET/CT for å vervifisere evt. fordeler med noen av modalitetene. Målet var nøyaktig TNM-staging	**Tverrsnittstudie** **52 pasienter med mistenkt eller biopsivervifisert NSCLC ble rekrutterting til studien. Alle pasientene ble undersøkt etter retningslinjer med EBUS, kontrast-CT og til slutt trimodal PET/CT + MR. 10 pasienter ble ekskludert etter at biopsi viste noe annet enn NSCLC.** **Datagrunnalget** **42 pasienter, 29 menn, 13 kvinner. Median alder 69 år (35-89)** **Bildene ble delt ut til to grupper med to nukleærmedisinere i hver gruppe. Begge gruppene analyserte monomodale PET-bilder, så analyserte gruppe A PET/CT-bildene, mens gruppe B analyserte PET/MR-bildene. Operatørene ble blindet for klinikk, bortsett fra mistanke om NSCLC.** **Utfall (outcome) validering** **(for eks. diagnose)** **Histologi utgjorde gullstandard for T og N-staging, mens andre bildemodaliteter ble brukt for M-staging, enten kontrast-CT eller kontrast-MR** **Statistiske metoder** **Forskjeller mellom TNM-klasifiseringen ut fra PET-bildene ble analysert med K-statistikk, mens forskjellene i TNM-klassifiseringen fra PET/CT og PET/MR-bildene ble analysert med Wilcoxon signed-ranked test.**	**Hovedfunn:** **Sammenlignet med PET/CT, ga PET/MR ekstra informasjon i 7 tilfeller i 5 pasienter (9%). Sammenlignet med PET/MR ga PET/CT ekstra informasjon i 18 tilfeller i 15 pasienter (36%)** **Bifunn**	**Styrke:** **Publiserer negativ data.** **Svakhet** **Studie delvis finansiert av GE-Healthcare, dog ingen ansatte i GE jobbet med studien elle behandling av data.** **Ikke alle primærtumorere ble resektert av etiske årsaker, men man har gjennom biopsi fått histologisk proøvemateriale fra alle tumorene.** **Hva diskutere forfatterne ?** **Muligheten for å bruke andre MR-protokoller i framtidige forsøk, men de tar så lang tid at det kan gå utover kvaliteten på PET-bilden.** **Denne studien brukte ikke kontrastagenser, så den må tolkes med forsiktighet når den sammenlignes med andre studier som bruker kontrast.**
Konklusjon **Begge modalitetene har lignende diagnostisk nøyaktighet, med en positiv trend for PET/CT. Med mulig unntak av hjerne- og levermetastaser vil PET/CT være den foretrukne modaliteten**			
Land **Sveits**			
År data innsamling **Mai 2012-november 2014**			

Referanse: de Bree, R., van der Putten, L., Van Tinteren, H., Wedman, J., Oyen, W. J., Janssen, L. M., ... & Hobbelink, M. G. (2016). Effectiveness of an 18 F-FDG-PET based strategy to optimize the diagnostic trajectory of suspected recurrent laryngeal carcinoma after radiotherapy: The RELAPS multicenter randomized trial. Radiotherapy and Oncology, 118(2), 251-256.	GRADE 4	
	Dokumentasjon	1b
	Anbefaling	A

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer
Evaluere 18F-FDG-PET som førstelinjediagnostikk ved residiverende lanrynxcancer i stedet for invasiv laryngoskopi med biopsi som er standard i dag. **Konklusjon** **Ved bruk av 18F-FDG-PET kan man redusere behovet for direkte laryngoskopi med 50% uten å senke kvaliteten på diagnostikken, eller øke dødligheten** **Land** **Nederland og Belgia** **År data innsamling** **Februar 2005 til februar 2009**	**Prospektiv randomisert studie. Ikke blindet.** **Deltakere ble rekruttert hvis de hadde mistenkt residiv minst 2 mnd etter (kjemo-)radioterapi. Mistanke med grunnlag av funn ved enten fleksibelt laryngoskopi eller ved symptomer.** **Eksklusjonskriterier var under 18 år, bevist residiv eller graviditet.** **Datagrunnlaget** **150 pasienter til sammen i alder. Randomisert i to grupper av dataprogram mtp å få to like store grupper i** **Utfall (outcome) validering** **Forskjell i antall unødvendige direkte laryngoskopier. Pasienter i PET-gruppen ble kun sendt til laryngoskopi hvis PET var positiv. Unødvendig laryngoskopi var definert som at det ikke ble oppdaget cancer i hverken første laryngoskopi eller i oppfølgingsperioden på 6 og 12 mnd** **Statistiske metoder** **Statistikken ble utført av en klinisk statistikker. Fisher's exact test ble brukt for å kalkulere hvor mange pasienter som trengtes i hver gruppe for å se en signifikant forskjell. Logistisk regresjon ble brukt for å se etter konfunderende forskjeller i røyking, alder og klinisk stadie i cancer før radiotesrapi. De to gruppene ble sammenlignet med Chi-kvadrat eller fisher's exact der hvor det var mer passende. T-test eller Wilcoxon ble brukt for å sammenligne kontinuerlige variabler.**	**Hovedfunn:** **En algoritme som inneholder PET(-CT) kan effektivt redusere antall unødvendige invasive prosedyrer med 50% uten å gå på bekostning av pasientsikkerhet og mulighet for å overse kreft. Det ble gjort et falsk negativt funn på PET, men dette ble oppdaget i CT-modaliteten i den bimodale skanneren. Dette er høyst uvanlig, da PET har høyere sensitivitet enn CT.** **Det var ingen forskjell i de pasientene som ble skannet med en PET- eller en PET/CT-skanner. Dette kan være pga det relativt lave antallet pasienter**	**Styrke:** **Den største styrken med denne studien er at den er randomisert og sammenligner to pasientgrupper i stedet for å ha en gruppe hvor man gjør begge undersøkelsene. Det er en multisenterstudie og man øker antallet pasienter og generaliserer prosedyrene i større grad, og derfor minsker sjansen for bias.** **Svakhet** **Studien var ikke blindet for hverken pasienter, leger eller annet personell som var med i studien. Det kan være vanskelig å se hvordan en slik studie skulle vært blindet. Da dette også ikke er basert på subjektive mål, mener jeg at mangelen på blinding ikke påvirker studien i negativ grad**