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"What are the (tumor) characteristics of patients visiting the Alexander Monro Hospital, a specialized clinic for breast care, in the years from 2013 to 2015 and to what extent have characteristics changed during these years?"

Bachelor thesis

Population of the Alexander Monro Hospital: trends over time and comparison to the national breast cancer population

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BORSTKANKER | BORSTAANDOENINGEN | ERFELIJKHEID

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Preface

This thesis is the conclusion of my Bachelor Program Health Sciences at the University of Twente. Moreover, it is a conclusion of my research conducted at the Alexander Monro Hospital (hereafter referred to as AMZ) in Bilthoven during the period September 2017 until February 2018.

The AMZ is the first specialized breast (cancer) hospital in the Netherlands. It was established by Jan van Bodegom in 2013, for different reasons. First, by establishing a focus clinic for breast (cancer) care, the aim was to offer patient-centered care in the most optimal way. Second, since breast (cancer) care is becoming more complex because of "microdiagnostics" and DNA research, highly specialized care was needed and this hospital has all their medical specialists under one roof, focusing on one disease. Even though the primary focus of this hospital is on breast cancer, other breast disorders can be diagnosed and treated in the AMZ as well. That means that benign breast deviations are also diagnosed and treated. Besides that, women with genetic predisposition and familial increased risk of breast cancer are also screened in the AMZ. This research focuses on the population of this hospital: the aim is to gain insights in demographics, patient characteristics and tumor characteristics.

Answering the research questions was not easy, but hard work, eventually, pays off. Fortunately, J. Felderhof was always there for me to answer my questions regarding the AMZ and my supervisors from the University of Twente, S. Siesling and J.A. van Til, were always willing to answer my queries regarding my report. I really appreciate the help many people gave me, both at the University of Twente and in the AMZ.

Moreover, my study advisor Anouk Prins deserves a particular note of thanks. Without her help the past 3.5 years, I could not have dealt with the challenges I faced during my bachelor program and I am very grateful for that. Lastly, I would like to thank my family for helping me to stay positive and keeping me motivated.

Nikki Luttikhuis, February 2018

Abstract

BACKGROUND Over the past decades, more focus clinics have been established in the Netherlands. The Alexander Monro Hospital in Bilthoven in 2013, the first and up to now only breast cancer hospital in the Netherlands, treating only patients with breast cancer or other lesions in the breasts, is an example of those focus clinics. Since assumption was made that the AMZ attracts patients from all regions in the Netherlands, insights in the (tumor) characteristics of these patients and demographics are valuable to see if these patients differ from the national breast cancer population. **OBJECTIVE** The aim of this study was to describe tumor characteristics, demographics and patient characteristics and determine whether change over the years has occurred. Besides that, tumor characteristics are being compared to the national breast cancer population. **DESIGN** Quantitative retrospective cohort. **POPULATION** The study population consists of all patients who have visited the AMZ from 2013 until 2015. Among these patients, tumor characteristics are gathered from patients who have been diagnosed with a malignant tumor and had treatment in the AMZ in the period of 2013-2015 **METHOD** Data of the patient characteristics is extracted from the personal health files of the patients and data of the tumor characteristics is extracted from the Netherlands Cancer Registry (NCR), which is hosted by the Netherlands Comprehensive Cancer Organization (IKNL). First, descriptive statistics was performed in order to gain insights in the patient characteristics, such as region, reason for visit, type of first contact, outcome and tumor characteristics, such as TNM classification, ER/PR/HER2 status, grade and so on. Next, the relationship between region and patient- and tumor characteristics was explored, such as type of first contact, TNM classification, grade and ER/PR/HER2 status. After that, a Two Way MANOVA was performed to show significant change between the years and finally a one-sample t-tests was performed to see if there was significant difference between the tumor characteristics of the patients in the AMZ and the national breast cancer population. **RESULTS** In total, 666 patients visited the hospital in 2013, 1308 in 2014 and 1368 in 2015. Over these years, most patients came from the regions Midden-Nederland, Utrecht/Rivierenland and Den Bosch, but around 55% of the patients visited the hospital from other regions. Most patients were new (65%), but many second opinions were requested in the AMZ as well (30%) and the remainder were patients with follow-up in the AMZ. The majority of the patients visited the hospital because they suspected breast cancer, 17% visited the hospital in order to receive their treatment in the AMZ and only 5% visited the AMZ to get screened. A benign tumor was most commonly diagnosed (43%), followed by breast cancer in 32% of the cases, the remaining patients were mostly diagnosed with no abnormalities. Most of those malign tumors were ductal and classified as T1 and N0. However, the majority of the patients were diagnosed with a grade II tumor (45%), in comparison with a grade I tumor (19%). The ER and PR status was mostly positive (respectively 74% and 59%), while the HER2 status was mostly negative (86%) and in total, 55 patients had a triple negative tumor. In 48% of the cases, patients had a breast-conserving surgery, compared to 52% of the patients with mastectomies. Patients with breast-conserving surgery had neoadjuvant treatment in 14%

of the cases and chemotherapy was offered most frequently in this neoadjuvant setting. Patients with mastectomies had neoadjuvant treatment in 29% of the cases, with chemotherapy as most frequent as well. Considering the adjuvant therapy, in the breast-conserving group 22% had chemotherapy, 35% hormonal therapy, 8% targeted therapy and 94% had radiotherapy. The patients with mastectomies had chemo-, hormonal-, targeted- and radiotherapy in respectively 28%, 44%, 15.9% and 20% of the cases. Looking into the relationship between region and patient- and tumor characteristics, faraway regions outside Utrecht and Midden-Nederland consisted of many second opinion seekers. Besides that, patients from Friesland, Zuidoost Brabant and Amsterdam had larger tumors and Friesland had more patients with a cN2 classification. Regarding the significant change over the years, significantly more patients visited the hospital for suspicion of breast cancer (for a second opinion) and more patients were diagnosed with a grade II tumor, but at the same time more patients had unknown grades. Besides that, less patients have received breast-conserving surgery over the years and less patients in the group of breast-conserving surgery have received adjuvant chemotherapy. Compared to the national breast cancer population, more patients were detected during the screening program. In addition, more patients were diagnosed with lobular and mixed tumors, carcinomas in situ, pN0 tumors, Grade II/III tumors and more patients received neoadjuvant treatment. In contrast, less patients were diagnosed with cT1, cT4, pT3, pN2, pN3 tumors, had positive ER and PR status and a negative HER2 status. Considering the treatment options, less patients had breast conserving surgery, and in this group, less patients had neoadjuvant chemotherapy and adjuvant hormonal therapy. Similarly, mastectomies were performed significantly more often and patients in this group had more neoadjuvant chemotherapy and adjuvant targeted therapy, but less (neo-)adjuvant hormonal therapy and adjuvant radiotherapy.

CONCLUSION Most new patients lived near the hospital and Den Bosch, second opinions lived further away. Patients seeking a second opinion are more likely to have a higher grade of the tumor. Over the years, more patients have visited the hospital for second opinions compared for example new patients, which could imply that patients value this specific oriented hospital as a second opportunity to gain more information about their diagnosis and/or treatment. Compared to the national breast cancer population, no valid conclusion can be drawn whether the AMZ has patients with less or more severe cases of breast cancer. Finally, more patients have received a mastectomy in the AMZ compared, adjuvant hormonal was given significantly less, but more insights should be gained in the reasons of the types of treatment prescribed.

1. Introduction

The AMZ is a specialized breast (cancer) care hospital in the Netherlands. In this hospital, all kinds of breast disorders can be diagnosed and treated. Even though the primary focus of the hospital and this research is on breast cancer, benign tumors are diagnosed in the AMZ as well. In this research, several benign tumors will be identified, but this will be further elaborated below.

1.1 Epidemiology

In the years 2013-2015 the total malignant tumor incidence rate among women in the Netherlands totaled respectively in 48.982 in 2013, 50.657 in 2014 and 50.710 in 2015. [1] Breast cancer represented about 35-40% in these total malignant tumor incidence rates among women, namely 16.897 cases in 2013, 19.889 in 2014 and 17.002 in 2015. [1] One third of the malignant tumors among women was located in the breast and this resulted in the fact that breast cancer is the most frequent form of cancer among women. [2] [3] In addition, the chance of developing a malignant breast tumor over these three years was approximately 12,5%, but this highly differentiates regarding the age of the patients. [4]

Apart from incidence rates of breast cancer, the mortality rates are of equal interest. For example, 3.197 women died because of breast cancer in 2013. [5] However, the risk of dying due to cancer has been decreasing in recent years: in the years 2011-2013, the survival rate, 5 years after diagnosis for an invasive carcinoma, was 88%. [1] [6] Besides mortality rates, prevalence rates can be considered as well. Prevalence rates show insights in the number of people that have been diagnosed in the past (for example five years ago) and who are still alive. [7] Breast cancer has the highest five-year prevalence rate with 20.1% of the top 10 most prevalent cancers in the Netherlands. [8]

1.2 Care trajectory

The high incidence of breast cancer in the Netherlands has resulted in the introduction of a screening-program to increase early detection of breast cancer. Women in the Netherlands between the ages of 50-75 are invited to participate in this screening-program every two years. [9] In 2014, in total 996.000 screening tests were performed and 24.430 women (24.5 out of 1000 women) were, because of these tests, referred to the hospital for further diagnostic research. Of these 24,5 out of 1000 woman, the majority (75%) did not get the diagnosis breast cancer. [10]

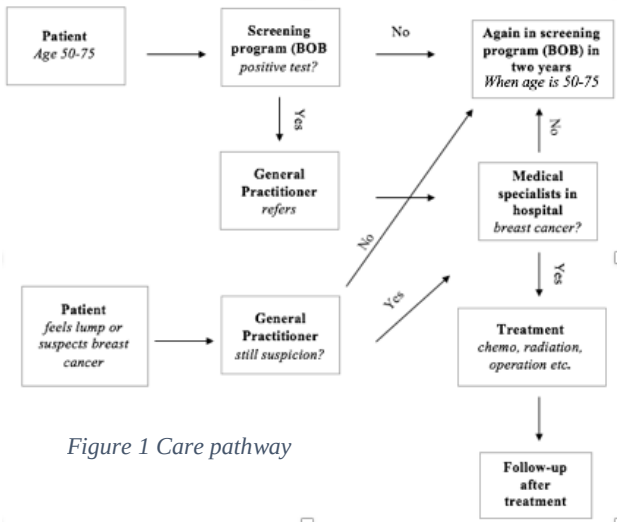

Figure 1 Care pathway

The suspicion of a breast tumor of women who do not get diagnosed through the screening program usually starts with the patient in terms of feeling pain, a palpable mass or other changes in the breast-area. Therefore, the general practitioner (GP), just as the screening program, plays an important role in the first steps towards a diagnosis of a breast tumor. [11]

There are several types of breast cancer. First, distinction is made between the invasive behavior of the tumor: either in situ of invasive. [12] [13] Besides that, distinction is made between the origin of the tumor: ductal and lobular. The lobular carcinomas start in the lobules, where milk is produced and the ductal carcinomas start in the milk ducts. [14] This leads (broadly) to four types of breast cancer: ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), lobular carcinoma in situ (LCIS), invasive lobular carcinoma (ILC) or a combination of those (mixed). Besides lobular and ductal carcinomas, tubular, medullar and mucinous breast carcinomas also occur in this research. There are more types of breast carcinomas, but these are indicated as other in this study.

In this research, several benign tumors will be identified. The most common form of benign breast tumors is a fibro adenoma. [15] Fibro adenomas represented, for example, 72% of palpable lesions in women under 30 years. [16] Besides that, mastopathy, cysts, benign (micro) calcifications, lipoma, papilloma and lipoid necrosis are examples of benign breast disorders that frequently occur.

After the diagnosis of a breast tumor (malignant and benign), the type of treatment is considered. Looking at the malignant breast tumors, local therapy and systemic therapy are offered. This leads to five most common types of breast cancer treatment: local therapy consists of operation and radiotherapy and systemic therapy consists of chemotherapy, hormonal therapy and targeted therapy. Targeted therapy is prescribed in situations with a positive HER-2 receptor and consists of, for example, trastuzumab. Most of the patients get a combination of these treatment options. [17] The treatment of a benign tumor depends on the kind of tumor and the discomfort experienced because of the tumor. Options are, for example, a regular check in the outpatient clinic or an operation to remove the tumor. [18] The referral patterns of breast cancer out of the screening program and the regular referral through general practitioners (GP) are shown in figure 1.

The diagnosis and treatment of breast cancer takes place in a hospital, which means that the suspicion of a (either malign or benign) breast tumor and trying to diagnose and treat these health issues medicalizes the patient directly. The GP, for example, is part of the Dutch Healthcare system and is directly paid by the health insurance companies. [19] From a legal perspective, the Dutch Healthcare system is based on four principal laws: The Health Insurance Law (ZVW), the Law of long-term Health Care (WLZ), Law of Social Support (WMO) and the Youth Law. [20] The Health Insurance Law ensures every citizen in the Netherlands of an all-round basic-package of healthcare. [21] All general and academic hospitals in the Netherlands provide insured health care. After being referred by for example a GP or the screening program (the screening program refers to the GP, who on their turn refers to, for example, a hospital), the hospitalization of a patient usually starts at either the outpatient clinic or the emergency room of a hospital. Direct hospitalization, without any referral, at the nursing department occurs rarely. [22] Hospitals in the Netherlands are subdivided into different types: general hospitals, categorical, top-clinical and academic hospitals. [23] The basic functions of these hospitals are diagnosis, therapy and nursing and all hospitals have, for example, an intensive care available. [22] Besides these kinds of hospitals, private institutions offer health care too, such as

private clinics and independent treatment centers (ZBC's). However, these private institutions also offer care that may not be reimbursed by health insurance companies. [24]

In some cases, patients doubt their diagnosis and/or the choices made regarding their treatment. These doubts could lead to seeking a second opinion from another medical specialist in another hospital. In order to be able to seek a second opinion, the patient needs a referral from his/her current physician (or GP). Patients can seek a second opinion on their own, without referral from their current physician, but most health insurance companies only reimburse a second opinion if the referral letter is available. [25] In the field of oncology, and especially breast cancer, second opinions have become an increasingly regular phenomenon, since diagnosis, treatment plans and prognosis are frequently a matter of life and death (literally). Moreover, medical information in this field is often complex and characterized by uncertainty. [26] There are several reasons why patients could seek a second opinion, such as internal locus of control, perceived health status and demanding to know all details of a treatment. [27] Patients primarily seek second opinions regarding their treatment options in 41.3% of the cases and in 34.8% in diagnostic concerns. [28]

1.3 Focus Clinics and the Alexander Monro Hospital

Lately, a lot of systematic functions of a general and academic hospital are being divided into smaller, specialized "focus clinics" situated within a hospital. [29] A focus clinic is designed to offer care around a certain disease, making use of the already composed health tracks. Therefore, the basic concepts of "routine", "standardization" and "focus" are at the heart of focus clinics. Making use of routines, standardization and focusing on one specialism should lead to better performance on quality and should reduce costs compared to a more complex environment where various types of specialisms are offered. [30] Besides that, establishment of specialized clinics should improve health outcomes as well. [31] [32]

The AMZ is a focus clinic, with the unique setting that it is not situated within a hospital and this is unique in the Netherlands. The AMZ aims to offer efficient, fast and accurate, integrated, patient centered health care and in order to meet the preferences of these patients, the care offered has several specific and unique features compared to other hospitals in the Netherlands. First, the AMZ offers diagnosis within 24 hours after the first consultation. Second, the dedicated specialists are all under one roof and focus on only one disease, and this centralization of services should lead to better outcomes in terms of efficient care. [31] Third, twice every day, the multidisciplinary tumor board takes place in order to deliver the patient a fast, and accurate, diagnosis and treatment plan. Several specialisms take place in this tumor board such as medical oncologists, oncologic surgeons, plastic surgeons, radiation oncologist, radiologists, pathologists, nurse practitioners, amongst others [33]. Fourth, not only the medical care is emphasized, but also the impact of the diagnosis breast cancer on the patient and family. At the start of the care provided, the psychic and social aspect of the care are handled too by planning consultations with the patients to pay attention to this aspect of care. [34] Last, besides these specific features of the care provided, the entire experience of visiting the hospital is specifically designed to

align to patients needs and preferences. For example, when entering the hospital, a hostess welcomes the patients and the character of the design of the waiting room is not the same other hospitals have. Besides that, the back office has glass walls, in order to keep contact with the patients easily. These concepts were designed to optimize the patient experience and the quality of life of the patients, since the environment where patients receive their care has been put central in designing the hospital.

Although being a focus clinic has multiple advantages, it also has its limitations. First, because of the scale of the hospital and the absence of other specialisms (for example a cardiology department), the AMZ does not have an Intensive Care present in the hospital. This leads to the fact that patients with an American Society of Anesthesiologists (ASA) score of three and higher cannot be treated in this hospital. This score aims to classify the health status of a patient, varying from I (a normal healthy patient) to IV (a declared brain-dead patient). The scores II and III represent patients with mild (II) and severe (III) systematic diseases. [35] More information about these scores can be found in Appendix I. Second, the hospital does not offer radiotherapy, because the maximum number of radiotherapy facilities is met and, besides that, since the benefits of offering radiotherapy on location did not outweigh the burden of building that kind of facility. Besides that, when establishing the hospital, the assumption was made that patients across the whole country would visit the hospital. Because the treatment of radiotherapy takes place every day, having radiotherapy in this hospital was regarded as too much of a burden due to travel distance. Collaboration with the UMC Utrecht provides the patients who do live close to Bilthoven to receive radiotherapy nearby and patients who live distant can receive radiotherapy in their own region. Besides that, radiotherapy is offered in all regions in the Netherlands and quality of these treatments does not fluctuate much. [36]

1.4 Aim of research and research question

As mentioned before, a focus clinic in general and in this case the AMZ has a high patient involvement and centralization of services and specialists. While there is strong assumption that the AMZ attracts patients from across the country and that these patients differ from the national population of cancer patients, there is no concrete data to support this. That is why this research aims to analyze several characteristics of the population of the AMZ from 2013 until 2015 (the new patients who have never visited the AMZ before), such as year of initial consultation, age, region in the Netherlands, referrer, type of first contact (new patient, 2nd opinion or follow-up), reasons for visiting, outcome (diagnosis). Besides benign tumor characteristics, insights in tumor characteristics of the patients with malignant tumors (documented by the Netherlands Cancer Registry (NCR)) who have entered a treatment pathway in the AMZ are examined in detail. Variables such as TNM, ER/PR/HER2 status and whether they received systemic (neo-) adjuvant treatment and radiotherapy are collected and will be compared to general numbers in order to analyze if the AMZ treats more (or less) advanced stages of breast cancer and if the policy regarding (neo-) adjuvant treatment differs from the national policy. More insights in demographics are gained: the connection between region and type of first contact, cT classification, cN

classification, grade and ER/PR/HER2 status will be explored. The variables collected of the patient characteristics and tumor characteristics will be analyzed separately per year. Moreover, the results of this research can be used to update and focus the marketing strategy of the hospital in order to attract more patients over the coming years.

This leads to the following research questions:

1. What are the patient characteristics, tumor characteristics and demographics of the patients visiting the AMZ in the period of 2013 to 2015?
2. To what extent have patient characteristics and tumor characteristics changed between 2013 and 2015?
3. Do the tumor characteristics of the patients visiting the AMZ differ from the general breast cancer population in the Netherlands?

3. Methodology

3.1 Study Design

The research proposed within this report will be conducted in the AMZ in Bilthoven, the Netherlands. This research is a quantitative retrospective research, since data from previous years (2013-2015) will be used in order to answer this research question. Data will be collected from the personal health files of the patients and the lists of the Netherlands Cancer Registry (NCR). [37]

3.2 Study Population and data collected

In order to answer the first research question, data of all 3370 patients who visited the AMZ from 2013-2015 will be collected. In this dataset, 28 patients were excluded, due to incomplete files, which leads to 3342 patients in total. Characteristics such as age at first visit and region in the Netherlands (demographics) were gathered. Besides that, the type of first contact was collected. When referring to type of first contact, the following definition is considered: the patient is either 1.) a new patient who has not had a previous diagnosis in another hospital and is referred to this hospital with a new problem to get a primary diagnosis, 2.) A patient who wants a second opinion about a previously made diagnosis or treatment option or 3.) Previously diagnosed and treated with/for a tumor and wants to continue her/his follow-up in this hospital. Furthermore, the reason for visiting was determined, which reflects the reason to go to a hospital in the first place. The options for this variable are: suspicion of breast cancer, screening because of (familial) increased risk for developing breast cancer (which differs from the national screening program) or taking over of treatment (or follow-up). After that, the outcome/diagnosis (malignant, benign, no abnormalities, cosmetic reasons, or no recurrent disease after having had a malign tumor in the past) was deduced along with type of benign tumor. All these variables were deduced from the personal health records of the patients.

In order to analyze the tumor characteristics, data of 603 malignant cases with a primary tumor who had treatment in the AMZ from 2013-2015 were requested from the Netherlands Cancer Registry (NKR). The Netherlands Cancer Registry is hosted by the Netherlands Comprehensive Cancer organization (IKNL). IKNL gathers data about all malignancies in hospitals in the Netherlands, including the AMZ. The main source of data notification is from the Automated Pathology archive and data is gathered directly from patient files by special trained registrars. In this research, variables such as cTNM, pTNM (both 7th edition), histological type, Estrogen receptor (ER), Progesterone receptor (PR), Human Epidermal Growth Factor receptor-type 2 (HER2), grade, type of operation and type of (neo-)adjuvant treatment. There were no data collected about the number of patients with distant metastasis (cM and pM), since the number of patients with distant metastasis that were treated in this hospital is very small. The data from the NKR shows that in 2013 104 patients have been diagnosed with a malignant tumor in the AMZ and had treatment within the AMZ, compared to 208 in 2014 and 290 in 2015. This means that 78%, 50% and 61% in respectively 2013, 2014 and 2015 of the total malign tumor population has had a primary diagnosis and has had treatment in the AMZ.

After these insights in the patient- and tumor characteristics are gained, the catchment area of the hospital is mapped. Demographics and patient- and tumor characteristics will be combined to see the relation between travel distance and other variables, such as type of first contact, TNM classification (cT, cN), grade and the receptor status.

After these data were collected, both datasets of the patient characteristics and the tumor characteristics are divided in separate groups based on the year of initial consultation in order to answer the second research question.

To answer the last research question, data of the national breast cancer population were collected to compare with the variables of the tumor characteristics. The variable "invasiveness" is excluded from this analysis, because the provided list with national percentages by the Netherlands Cancer Registry does not distinguish between invasiveness with or without DCIS (while in this study we did distinguish between invasiveness with or without DCIS, see table 3). The data regarding the treatment options are standardized to metastasis: the patients with distant metastasis were excluded in the dataset of the national breast cancer population, because the number of patients with distant metastasis in the AMZ is very small (1-5 patients per year) and since having distant metastasis plays an important role in the kind of treatment offered, this influences the internal validity.

In summary, there are two databases. The first database consists of all patients who had their initial visit in the AMZ in the years from 2013-2015 and this database consists both patients with a benign diagnosis and malignant diagnosis. The second database only consists patients who have had a primary malignant diagnosis and had treatment in the AMZ from 2013-2015.

3.3 Statistical analysis

Data were analyzed to determine tumor characteristics and the characteristics of the patients who visited the AMZ by making frequency tables using SPSS Statistics 24. Besides that, the years 2013, 2014, and 2015 were analyzed separately, to see if change in the characteristics has occurred over the years, using a Two Way MANOVA. After this analysis has been performed, these numbers were compared to general numbers of breast cancer tumor characteristics in the Netherlands using the cancer registration numbers of NKR, using a two-tailed one sample t test. [37] In order to gain insights in demographics of patients, Tableau Desktop was used. In this research, alpha of 0.05 is used to show significance.

4. Results

4.1 Patient characteristics and tumor characteristics

The patient background characteristics are shown in table 1. In 2013, 666 patients visited the AMZ, in 2014 1308 patients and in 2015 1368 patients. The ZIP-codes derived from the personal health files were translated into regions in the Netherlands. [38] As can be seen in figure 2, the regions Midden-Nederland, Utrecht/Rivierenland and Den Bosch are represented most frequently throughout the years 2013-2015. Clear distinction of the regions can be found in Appendix III.

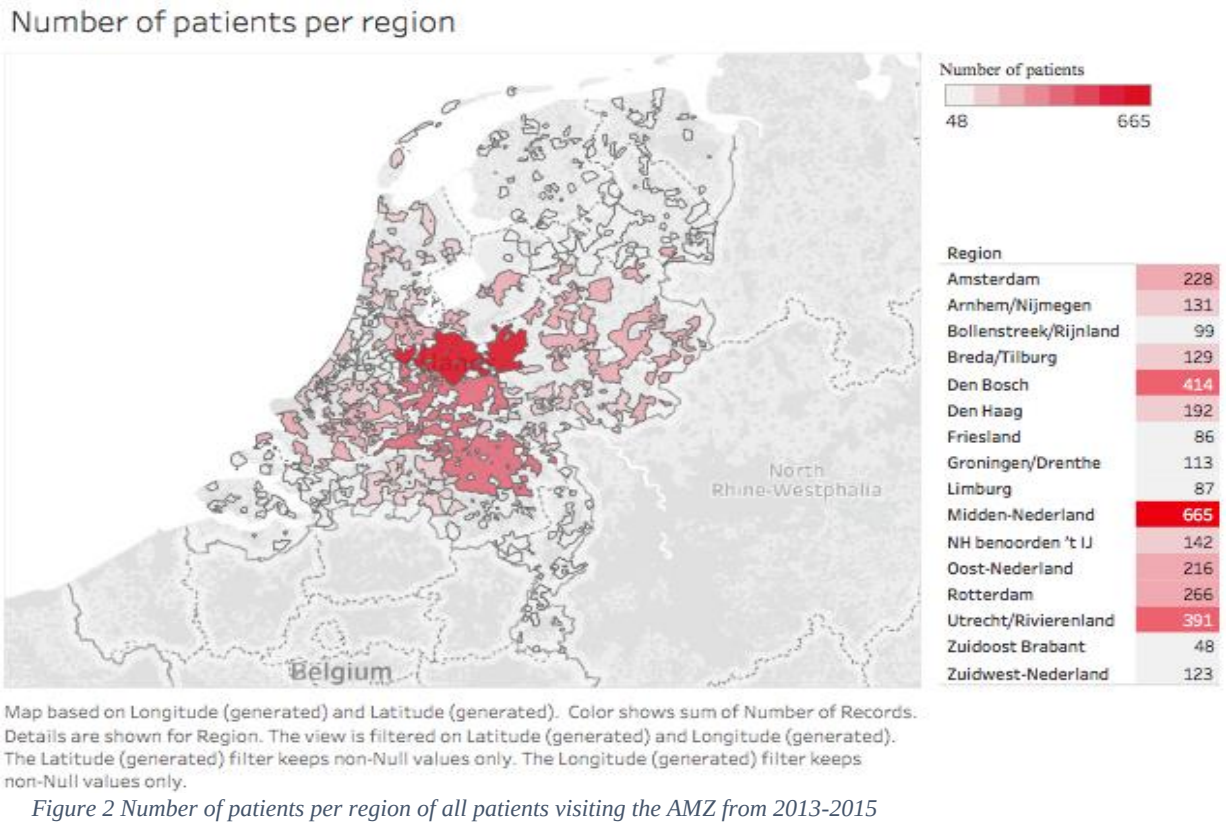

Figure 2 Number of patients per region of all patients visiting the AMZ from 2013-2015

As shown in table 1, the mean age at first visit over the years was approximately 50. Throughout all the years, most patients were new patients, with respectively 71%, 61.4% and 63.3% of total patients. The remainder of the patients were either patients that were there for a 2nd opinion or follow-up care.

The most important reason for the patients visiting the hospital was suspicion of breast cancer (either new or a 2nd opinion), while only 5% visited the hospital for a screening (apart from the national screening program).

		2013 (n=666)	**2014** (n=1308)	**2015** (n=1368)	**p-value***
Age at first visit	Mean (SD)	49.48 (11.866)	50.16 (12.156)	50.67 (11.775)	0.745
Region	Count				0.977
Amsterdam	n(%)	34 (5.1)	89 (6.8)	105 (7.7)	
Arnhem/Nijmegen	n(%)	20 (3.0)	57 (4.4)	54 (3.9)	
Bollenstreek/Rijnland	n(%)	18 (2.7)	49 (3.7)	32 (2.3)	
Breda/Tilburg	n(%)	27 (4.1)	52 (4)	50 (3.7)	
Den Bosch	n(%)	117 (17.6)	128 (9.8)	169 (12.4)	
Den Haag	n(%)	36 (5.4)	84 (6.4)	72 (5.3)	
Friesland	n(%)	26 (3.9)	20 (1.5)	40 (2.9)	
Groningen/Drenthe	n(%)	18 (2.7)	48 (3.7)	47 (3.4)	
Limburg	n(%)	19 (2.9)	40 (3.1)	28 (2)	
Midden-Nederland	n(%)	114 (17.1)	282 (21.6)	269 (19.7)	
Noord-Holland (NH) benoorden 't IJ	n(%)	20 (3)	64 (4.9)	58 (4.2)	
Oost-Nederland	n(%)	35 (5.3)	83 (6.3)	98 (7.2)	
Rotterdam	n(%)	69 (10.4)	93 (7.1)	104 (7.6)	
Utrecht/Rivierenland	n(%)	80 (12)	136 (10.4)	175 (12.8)	
Zuidoost Brabant	n(%)	9 (1.4)	20 (1.5)	19 (1.4)	
Zuidwest-Nederland	n(%)	21 (3.2)	57 (4.4)	45 (3.3)	
Unknown	n(%)	3 (0.5)	6 (0.5)	3 (0.2)	
Type of first contact	Count				0.059
New Patient	n(%)	473 (71)	803 (61.4)	866 (63.3)	
2nd Opinion	n(%)	126 (18.9)	448 (34.3)	468 (34.2)	
Follow-Up	n(%)	64 (9.6)	57 (4.4)	34 (2.5)	
Other	n(%)	1 (0.2)	0 (0)	0 (0)	
Unknown	n(%)	2 (0.3)	0 (0)	0 (0)	
Referrer	Count				0.000
General Practitioner	n(%)	398 (59.8)	388 (29.7)	352 (25.7)	
Screening Program	n(%)	78 (11.7)	161 (12.3)	229 (16.7)	
Unknown	n(%)	190 (28.5)	759 (58)	787 (57.5)	
Reason for visiting	Count				0.046
Suspicion breast cancer	n(%)	439 (65.9)	750 (57.3)	748 (54.7)	
2nd opinion/suspicion breast cancer	n(%)	71 (10.7)	269 (20.6)	320 (23.4)	
2nd opinion/taking over treatment	n(%)	118 (17.7)	225 (17.2)	219 (16)	
Screening	n(%)	37 (5.6)	64 (4.9)	81 (5.9)	
Unknown	n(%)	8 (1.2)	0 (0)	0 (0)	

Table 1 Background patient characteristics of all patients visiting the AMZ between 2013-2015

* Two Way MANOVA is performed, significance is shown

With regard to disease characteristics (table 2), the majority of the patients (77%) did not have a previous diagnosis in the breast. Most patients (40-45%) received a benign diagnosis, but malign tumors also represented 30-35% of the diagnosis and around 18% of the patients did not have any abnormalities in the breast area. The number of benign tumors over the years was respectively 303, 555 and 549 and cysts had the largest share in these benign tumors. Besides that, benign calcifications

(approximately 15-25%), mastopathy (10-16%) and fibro adenomas (approximately 12%) occurred frequently as well. Besides that, 2-5% of the patients got a plastic surgery advised (cosmetic reasons), because of for example genetic predisposition. Additional analysis regarding age and diagnosis is shown in Figure 11 in Appendix IV.

		2013 (n=666)	**2014** (n=1308)	**2015** (n=1368)	**p-value***
Previous breast disease	Count				0.746
No/Unknown	n(%)	518 (77.8)	1011 (77.3)	1047 (76.5)	
Benign	n(%)	70 (10.5)	198 (15.1)	209 (15.3)	
Malign	n(%)	78 (11.7)	99 (7.6)	112 (8.2)	
Outcome	Count				0.215
Benign	n(%)	303 (45.5)	555 (42.4)	549 (40.1)	
Malign	n(%)	134 (29)	418 (32)	478 (34.9)	
No abnormalities	n(%)	116 (17.4)	250 (19.1)	247 (18.1)	
Recurrent disease	n(%)	37 (5.6)	31 (2.4)	18 (1.3)	
Cosmetic reasons	n(%)	12 (1.8)	50 (3.8)	68 (5)	
Other	n(%)	0 (0)	0 (0)	4 (0.3)	
Unknown	n(%)	4 (0.6)	4 (0.3)	4 (0.3)	
Type benign tumor	Count	**n=303**	**n=555**	**n=549**	0.059
Fibro adenoma	n(%)	38 (12.5)	68 (12.3)	64 (11.7)	
Mastopathy	n(%)	49 (16.2)	54 (9.7)	76 (13.8)	
Cysts	n(%)	97 (32)	195 (35.2)	224 (40.8)	
Benign calcifications	n(%)	48 (15.8)	140 (25.3)	102 (18.6)	
Lipoma	n(%)	13 (4.3)	16 (2.9)	9 (1.6)	
Papilloma	n(%)	1 (0.3)	8 (1.4)	2 (0.4)	
Lipoid necrosis	n(%)	0 (0)	4 (0.7)	5 (0.9)	
Other	n(%)	31 (10.2)	65 (11.7)	62 (11.3)	
Unknown	n(%)	26 (8.6)	4 (0.7)	5 (0.9)	

Table 2 Disease characteristics of all patients visiting the AMZ 2013-2015

* Two Way MANOVA was performed, significance is shown

As mentioned before, the data from the NKR show that in 2013 104 patients have been diagnosed with a malignant tumor and had treatment in the AMZ, compared to 208 in 2014 and 290 in 2015 (table 3). The age at first visit of these patients was between 53-55 years and approximately 40% of these patients cancer was detected during participation in the national screening program. Looking at the invasiveness of the tumors, 10-14% was non-invasive over the years, which means the majority was invasive, either with or without DCIS. When looking at the cTNM and pTNM, most of the tumors were T1 and T2, N0 and N1. When considering the histological type of the tumors, this analysis also shows the ductal type as most frequent (ca. 80-90%). Looking at the grade, grade II and III mostly occur. The ER status was mostly positive (67-79%) over all the years, the PR status was in 55%-63% of the cases positive and the HER-2 status was, in contrast, only positive in 25-30% of the cases.

		2013 (n=104)	**2014** (n=208)	**2015** (n=290)	**p-value***
Age at first visit	Mean (SD)	53.17 (9.340)	54.70 (10.414)	54.63 (10.489)	0.404
Referred by screening	Count				0.715
No	n(%)	60 (57.7)	130 (62.5)	177 (61)	
Yes	n(%)	44 (42.3)	78 (37.5)	113 (39)	
Invasive	Count				0.216
Only DCIS	n(%)	12 (11.5)	24 (11.5)	41 (14.1)	
Invasive without DCIS	n(%)	31 (29.8)	89 (42.5)	110 (37.9)	
Invasive with DCIS	n(%)	61 (58.7)	95 (45.7)	139 (47.9)	
Histological type	Count				0.054
Ductal	n(%)	91 (87.5)	178 (85.6)	230 (79.3)	
Lobular	n(%)	7 (6.7)	23 (11.1)	27 (9.3)	
Both lobular and ductal	n(%)	1 (1)	2 (1)	24 (8.3)	
Mucinous	n(%)	2 (1.9)	3 (1.4)	2 (0.7)	
Medullar	n(%)	0 (0)	2 (1)	1 (0.3)	
Tubular	n(%)	2 (1.9)	0 (0)	3 (1)	
	n(%)	1 (1)	0 (0)	3 (1)	
cT					0.349
Unknown	n(%)	2 (1.9)	4 (1.9)	2 (0.7)	
No tumor discovered	n(%)	0 (0)	1 (0.5)	0 (0)	
Carcinoma in situ	n(%)	17 (16.3)	30 (14.4)	55 (19)	
T1	n(%)	51 (49)	79 (38)	125 (43.1)	
T2	n(%)	25 (24)	76 (36.5)	83 (28.6)	
T3	n(%)	9 (8.7)	17 (8.2)	23 (7.9)	
T4	n(%)	0 (0)	1 (0.5)	2 (0.7)	
cN	Count				0.499
Unknown	n(%)	0 (0)	0 (0)	1 (0.3)	
N0	n(%)	83 (79.8)	166 (79.8)	237 (81.7)	
N1	n(%)	19 (18.3)	32 (15.4)	43 (14.8)	
N2	n(%)	0 (0)	5 (2.4)	7 (2.4)	
N3	n(%)	2 (1.9)	5 (2.4)	2 (0.7)	
pT	Count				0.760
Unknown	n(%)	1 (1)	7 (3.4)	2 (0.7)	
No tumor discovered	n(%)	9 (8.7)	9 (4.3)	16 (5.5)	
Carcinoma in situ	n(%)	12 (11.5)	24 (11.5)	41 (14.1)	
T1	n(%)	53 (51)	106 (51)	169 (58.3)	
T2	n(%)	29 (27.9)	57 (27.4)	56 (19.3)	
T3	n(%)	0 (0)	5 (2.4)	6 (2.1)	
T4	n(%)	0 (0)	0 (0)	0 (0)	
pN	Count				0.107
Unknown	n(%)	6 (5.8)	4 (1.9)	10 (3.4)	
N0	n(%)	71 (68.3)	151 (72.6)	225 (77.6)	
N1	n(%)	25 (24)	44 (21.2)	49 (16.9)	
N2	n(%)	2 (1.9)	6 (2.9)	4 (1.4)	
N3	n(%)	0 (0)	3 (1.4)	2 (0.7)	
Grade	Count				0.015
Grade I	n(%)	20 (19.2)	39 (18.8)	60 (20.7)	
Grade II	n(%)	43 (41.3)	93 (44.7)	134 (46.2)	
Grade III	n(%)	26 (25)	52 (25)	80 (27.6)	
Unknown	n(%)	15 (14.4)	24 (11.5)	16 (5.5)	
ER Status	Count				0.631

Negative	n(%)	9 (8.7)	42 (20.2)	30 (10.3)	
Positive	n(%)	83 (79.8)	141 (67.8)	218 (75.2)	
Unknown	n(%)	12 (11.5)	25 (12)	42 (14.5)	
PR Status	Count				0.630
Negative	n(%)	30 (28.8)	68 (32.7)	65 (22.4)	
Positive	n(%)	62 (59.6)	115 (55.3)	183 (63.1)	
Unknown	n(%)	12 (11.5)	25 (12)	42 (14.5)	
HER2 Status	Count				0.613
Not determined	n(%)	1 (1)	1 (0.5)	1 (0.3)	
Positive	n(%)	19 (18.3)	28 (13.5)	28 (9.7)	
Negative	n(%)	72 (69.2)	155 (74.5)	218 (75.2)	
2+	n(%)	0 (0)	0 (0)	2 (0.7)	
Unknown	n(%)	12 (11.5)	24 (11.5)	41 (14.1)	

* Two Way MANOVA was performed, significance is shown

Table 3 Tumor characteristics patients with primary malignant diagnosis and operation visiting the AMZ 2013-2015

As can be seen in table 4, first, distinction is made in the kind of surgery performed: breast-conserving or a mastectomy. In 2013, 59 patients had breast-conserving surgery, compared to 92 in 2014 and 122 in 2015. Of these patients, 13-15% had neoadjuvant treatment before their breast-conserving operation: 8-11% of the patients had neoadjuvant chemotherapy, 1-4% had neoadjuvant hormonal therapy and 1-4% had neoadjuvant hormonal and targeted therapy. Adjuvant treatment was offered more frequently among the patients with breast-conserving surgery: 15-30% had chemotherapy, 27-44% had hormonal therapy, 4-12% had targeted therapy and 90-98% received radiotherapy. Besides this group of patients, 45 patients in 2013, 115 in 2014 and 168 in 2015 had a mastectomy in the AMZ. In total, neoadjuvant therapy was given in 27-30% of these patients, of which 21-25% chemotherapy and 4-7% chemo- and targeted therapy. Adjuvant chemotherapy was given to 20-32% of the patients, adjuvant hormonal therapy to 38-47%, targeted therapy to 10-23% and radiotherapy to 20% of the patients.

		2013 (n=104)	**2014** (n=207)	**2015** (n=290)	**p-value***
Breast-conserving surgery	**n (% of total n)**	**59 (56.73)**	**92 (44.23)**	**122 (42.07)**	0.033
Neoadjuvant:	n (% of total n breast-conserving surgery)	8 (13.56)	13 (14.13)	18 (14.75)	0.976
Only chemotherapy	n (% of total n breast-conserving surgery)	5 (8.47)	10 (10.87)	14 (11.48)	0.818
Only hormonal therapy		2 (3.39)	1 (1.09)	2 (1.64)	0.932
Only targeted therapy		-	-	-	-
Only radiotherapy		-	-	-	-
Chemo- and hormonal		-	-	-	-
Chemo- and targeted		2 (3.39)	2 (2.17)	2 (1.64)	0.760
Hormonal and targeted		-	-	-	-
Adjuvant:					-
Adj. Chemotherapy	n (% of total n breast-conserving surgery)	18 (30.51)	18 (19.57)	19 (15.57)	0.047
Adj. Hormonal therapy		26 (44.08)	25 (27.17)	41 (33.61)	0.102
Adj. Targeted therapy		7 (11.86)	8 (8.7)	5 (4.1)	0.147
Adj. Radiotherapy		55 (93.22)	90 (97.83)	112 (91.8)	0.224
Mastectomy:	**n (% of total n)**	**45 (43.27)**	**115 (55.56)**	**168 (57.93)**	0.35
Neoadjuvant:	n (% of total n mastectomy)	13 (28.89)	32 (27.83)	50 (29.76)	0.94

Only chemotherapy	n (% of total n mastectomy)	11 (24.44)	26 (22.61)	36 (21.43)	0.915
Only hormonal therapy		-	-	3 (1.79)	0.236
Only targeted therapy		-	-	-	-
Only radiotherapy		-	-	-	-
Chemo- and hormonal		-	-	-	-
Chemo- and targeted		2 (4.44)	6 (5.22)	11 (6.55)	0.816
Targeted- and hormonal		-	-	-	-
Adjuvant:					-
Adj. Chemotherapy	n (% of total n mastectomy)	14 (31.11)	35 (30.43)	35 (20.83)	0.103
Adj. Hormonal therapy		20 (45.45)	54 (46.96)	64 (38.1)	0.337
Adj. Targeted therapy		10 (22.22)	17 (14.78)	18 (10.71)	0.132
Adj. Radiotherapy		9 (20)	23 (20)	35 (20.83)	0.977

Table 4 Treatment options of patients with primary malignant diagnosis and operation in the AMZ from 2013-2015

* Two Way MANOVA was performed, significance is shown

In addition, table 5 shows the type of first contact in relation to the size of the tumor. The patients who visited the AMZ as a new patient, mostly had a T1 tumor, followed by a T2 tumor. Likewise, most of the patients who came to the hospital for a second opinion had a T1 tumor, followed by T2 tumors as well. However, the patients who had their follow-up in the AMZ, were mostly diagnosed with T2 and T3 tumors. There was no significant difference between the three types of first contact regarding the size of the tumor.

	Carcinoma in situ	**No tumor discovered**	**T1**	**T2**	**T3**	**T4**	**Unknown**	**p-value***
New patient	17.18%	-	45.42%	27.10%	9.16%	0.38%	0.76%	0.14
2nd Opinion	16.92%	0.30%	40.48%	33.23%	6.65%	0.60%	1.81%	
Follow-up	11.11%	-	22.22%	33.33%	33.33%	-	-	

Table 5 Type of first contact of patients with primary malignant diagnosis and operation in the AMZ from 2013-2015 in relation to size of tumor

* Two Way ANOVA performed, significance is shown

4.1.1 Relation between region and patient- and tumor characteristics

First of all, as can be seen in table 6, figure 3 and table 7 are extracted from the database of the patient characteristics. Next to that, table 8 and figures 4,5,6,7,8 and 9 are extracted from the database of the tumor characteristics. Besides that, the number of patients coming from each region is shown separately per database.

	Patient characteristics: all patients 2013-2015	**Tumor characteristics: primary tumor and operation2013-2015**
Figures/tables	Figure 3, table 7	Table 8, Figure 4,5,6,7,8,9
Grand total	3330	602
Regions		
Amsterdam	228	28
Arnhem/Nijmegen	131	22
Bollenstreek/Rijnland	99	17

Breda/Tilburg	129	32
Den Bosch	414	95
Den Haag	192	43
Friesland	86	13
Groningen/Drenthe	113	33
Limburg	87	18
Midden-Nederland	665	87
NH benoorden 't IJ	142	20
Oost-Nederland	216	51
Rotterdam	266	45
Utrecht/Rivierenland	391	60
Zuidoost Brabant	48	11
Zuidwest-Nederland	123	27

Table 6 Database of each figure and table and number of patients per region

As can be seen in Figure 3, the patients who visit the hospital as a new patient are mostly from the regions Utrecht/Rivierenland, Midden-Nederland and Den Bosch. The second opinions, however, are more spread nationwide. The percentages show that the regions Breda/Tilburg, Friesland, Groningen/Drenthe, Limburg and especially Zuidoost Brabant consist of relatively more patients visiting the hospital for a second opinion (more than 40%). Patients who visit the AMZ for follow-up are mostly from Den Bosch.

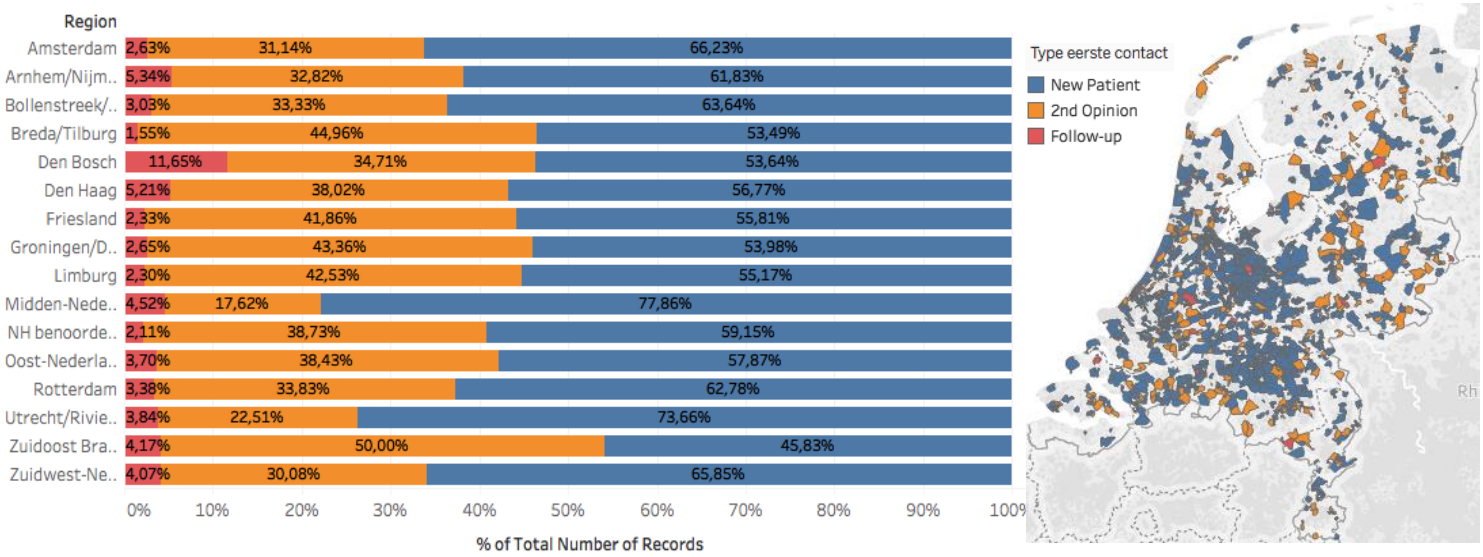

Figure 1 Relation between type of first contact of all patients visiting the AMZ from 2013-2015and region with percentages

These results lead to the fact that there is a significant relation shown between living in a faraway region and seeking a second opinion. As can be seen in table 7, less patients from the regions Utrecht/Rivierenland and Midden-Nederland (regions close to the AMZ) visit the hospital for a second opinion, compared to patients from other regions in the Netherlands. In addition, patients visiting the hospital for a second opinion (from all regions) are more likely to be diagnosed with a tumor with a higher differentiation grade (see table 8).

	Utrecht/Rivierenland or Midden-Nederland (n=1470)	**Other region** (n=1872)	**p-value***
Second opinion	348	694	0.000
Other type of first contact	1122	1178	

Table 7 Type of first contact of all patients visiting the AMZ from 2013-2015 in relation to living in a faraway region

* Two way ANOVA is performed, significance is shown

	2nd Opinion (n=331)	**Other type of first contact** (n=271)	**p-value***
Grade I	56	63	0.044
Grade II	150	120	
Grade III	89	69	
Unknown	36	19	

Table 8 Type of first contact of patients with primary malignant diagnosis and operation in the AMZ from 2013-2015 in relation to grade

* Two way ANOVA is performed, significance is shown

In figure 4 is the relation between the size of the tumor (cT) and the residence of the patients shown. The patients from the regions Friesland, Zuidoost Brabant and Amsterdam turned out to have larger tumors (cT3 and cT4) compared to other regions. The region Groningen/Drenthe, on the other hand, did not consist of any patient with a cT3 tumor. Carcinomas in situ were represented relatively more frequent in the regions Friesland and NH benoorden ‘t IJ and the regions Bollenstreek/Rijnland and Breda/Tilburg consisted of many patients with a cT1 tumor.

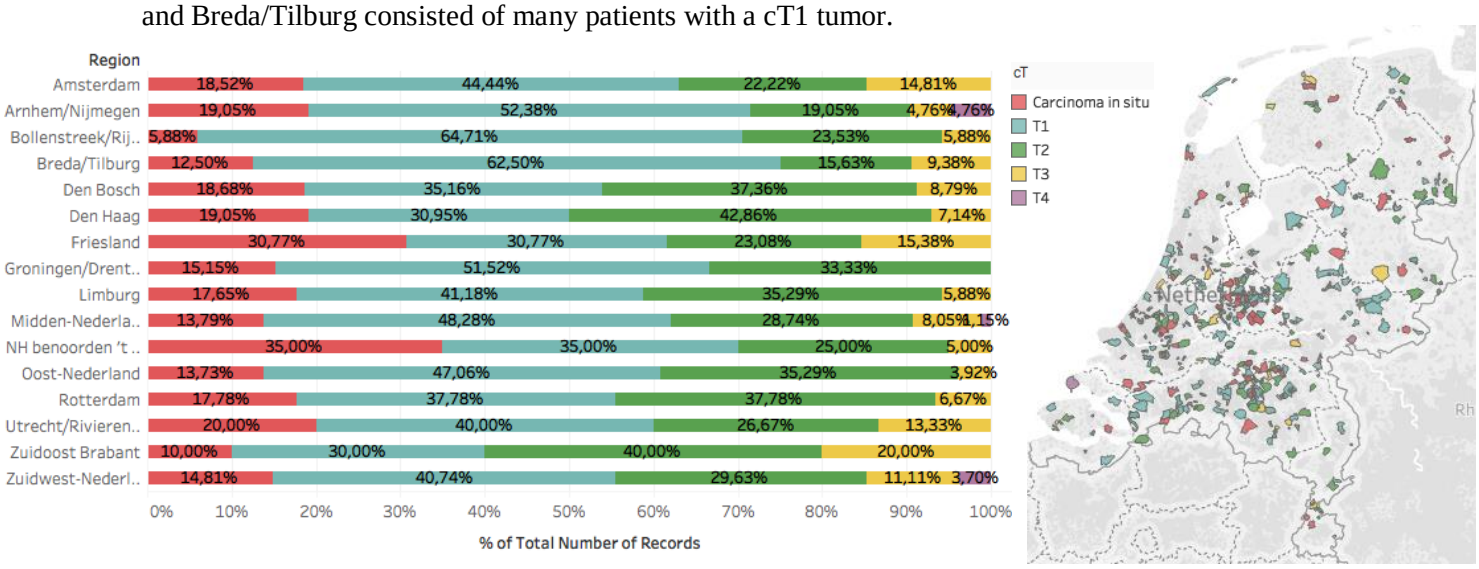

Figure 4 cT of patients with primary malignant diagnosis and treatment in the AMZ from 2013-2015 in relation to region

As shown in figure 5, patients from the regions Bollenstreek/Rijnland, Friesland and Zuidoost Brabant had relatively more affected lymph nodes, compared to other regions. Especially Friesland consisted of patients with more severe cases, since 15,38% of the patients had a cN2 classification. Besides that, in Zuidwest Nederland 7.41% of the patients was classified with a cN3 tumor, whereas other regions only had a couple of patients with this classification.

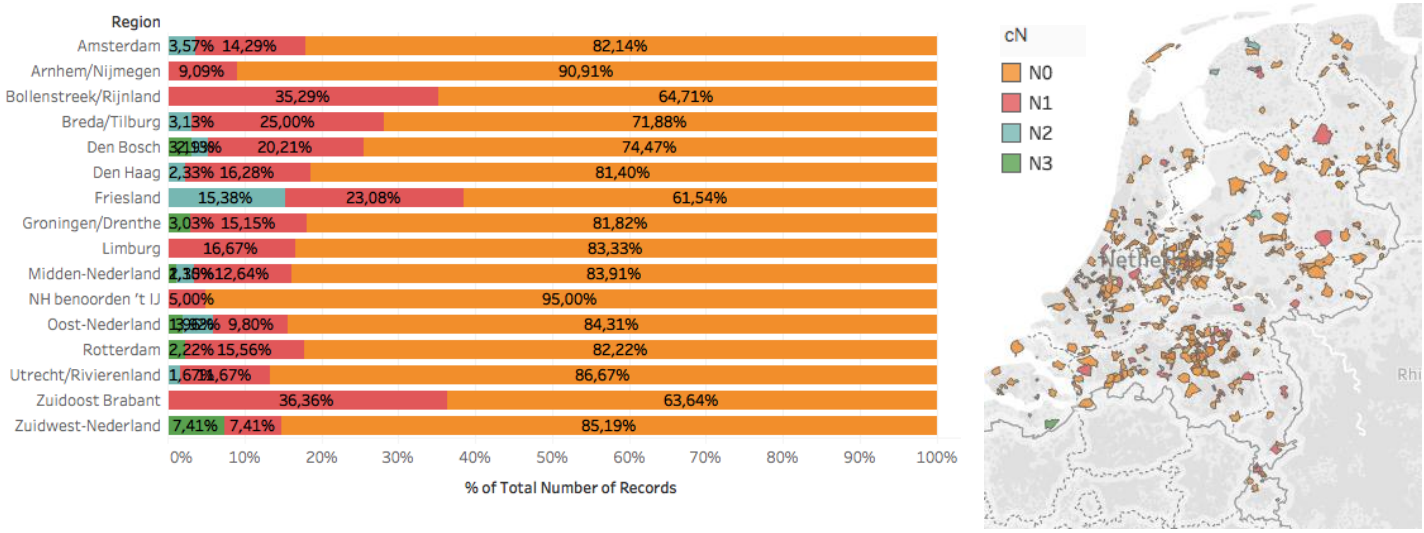

Figure 2 cN of patients with primary malignant diagnosis and treatment in the AMZ from 2013-2015 in relation to region

The association of the region of the patients with the grade of the tumor is shown in figure 6. In the regions Limburg, NH benoorden 't IJ, Utrecht/Rivierenland and Zuidoost Brabant more than 85% of the patients has been diagnosed with grade II or III tumors. In addition, 40% of the patients in Friesland and 34% of the patients in Breda/Tilburg had a grade III tumor.

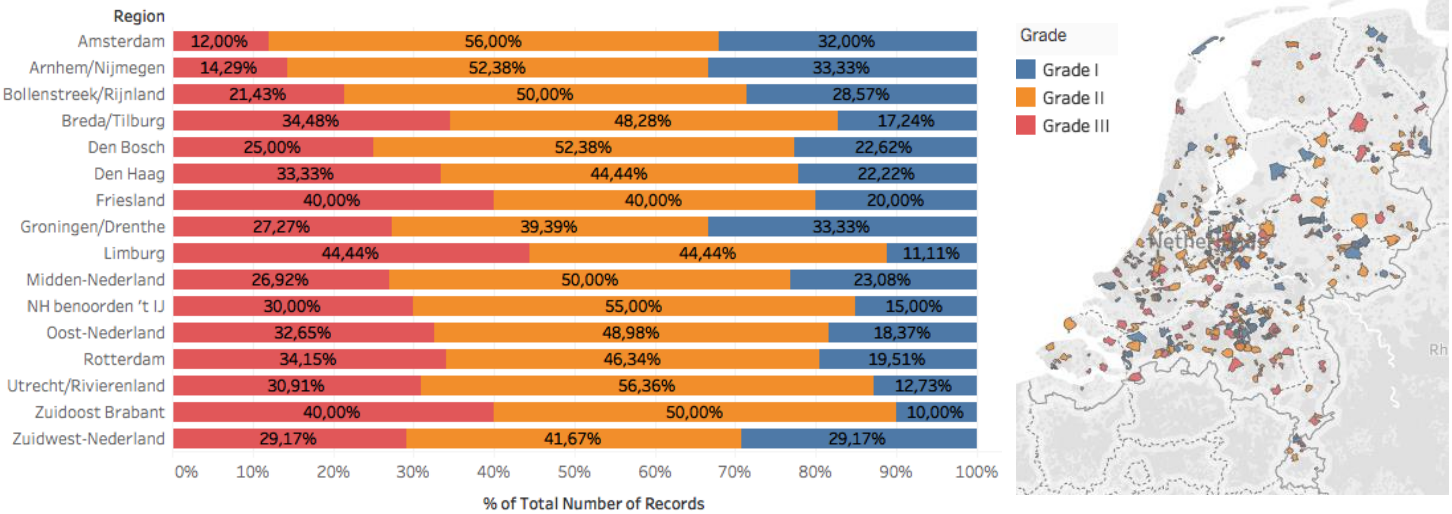

Figure 3 Grade of patients with primary malignant diagnosis and treatment in the AMZ from 2013-2015 in relation to region

Finally, the relation between ER/PR/HER2 receptor status and the region is outlined. Figure 7, 8 and 9 show the ER/PR/HER2 status in combination with the region. Considering the ER, Limburg consisted of many patients with a negative status, whereas the patients from Amsterdam and Bollenstreek/Rijnland mostly had a positive ER status. In general, there was not much differentiation between the regions regarding the PR status, but the regions Arnhem/Nijmegen, Friesland and Limburg had relatively more patients with a negative PR status and, on the other hand, the regions Oost-Nederland and NH benoorden 't IJ consisted of relatively more patients with a positive PR status. The HER2 status in relation to region shows that in general not much differentiation occurs in the regions, but Groningen/Drenthe, Bollenstreek/Rijnland, Zuidoost Brabant and Zuidwest Nederland turned out to have more patients with a negative HER2 status. In table 14 in Appendix IV, the additional analysis of the triple negatives (having a negative ER, PR and HER2 status in one tumor) in relation to the region is shown.

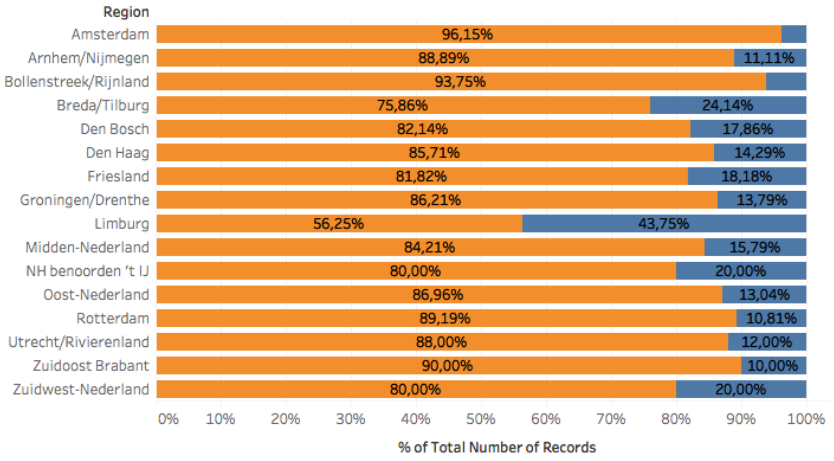

Figure 4 ER status of patients with primary malignant diagnosis and treatment in the AMZ from 2013-2015 in relation to region

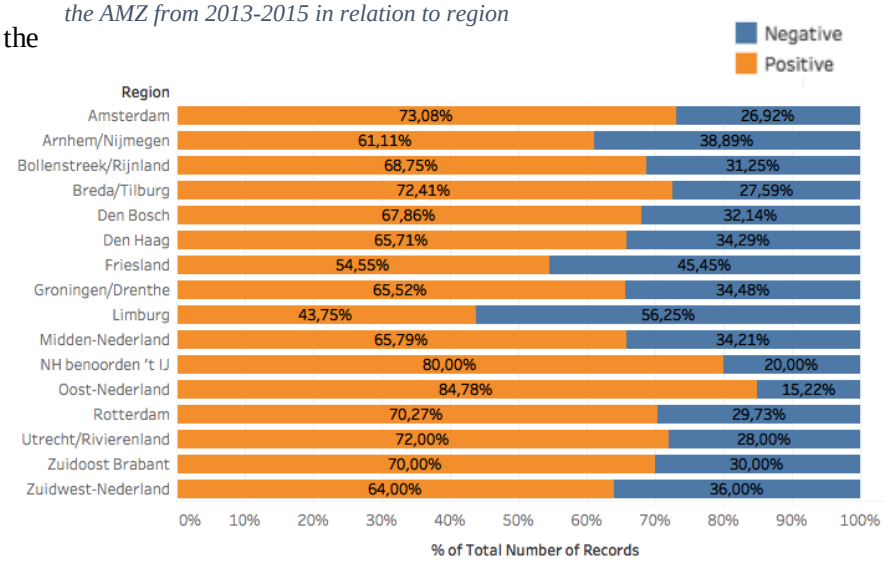

Figure 8 ER status of patients with primary malignant diagnosis and treatment in the AMZ from 2013-2015 in relation to region

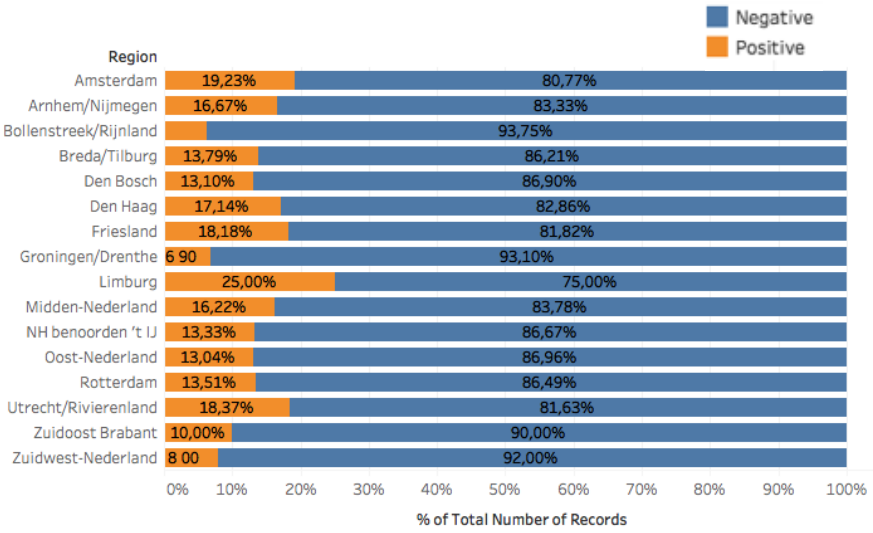

Figure 9 HER2 status of patients with primary malignant diagnosis and treatment in the AMZ from 2013-2015 in relation to region

4.2 Change over time

The insights in patient- and tumor characteristics as shown in the previous paragraph have been analyzed separately per year in order to track the changes over time, shown in table 1,2,3 and 4 in the last column. As can be seen in table 1, the variables referrer and reasons for visiting show significant change over time: more referrers were unknown and more patients visited the hospital for a second opinion regarding their diagnosis. Besides that, as shown in table 3 there has been significant change over time in the grade of the tumor: more grade I and II tumors have been diagnosed, but at the same time there were more unknown grades. Finally, the treatment variables shown in table 4 have significantly changed two times: less patients have received breast-conserving surgery over the years and less patients in the group of breast-conserving surgery have received adjuvant chemotherapy.

4.3 Differences with national breast cancer population

Finally, the tumor characteristics of 602 patients over the three years were compared to tumor characteristics of the national breast cancer population. As shown in table 9, the mean age of the patients in the AMZ is significantly younger with a mean age of 51.41 compared to the national average age at which patients receive a breast cancer diagnosis (mean age is 62.03). Next to this, significantly more patients in the AMZ were diagnosed with cancer during participation in the screening program. The TNM classification shows that significantly more tumors were classified as in situ and cT3, less tumors were classified as cT1 and cT4 and the cT2 tumors did not show significant difference. In the AMZ, the N2 classification occurred significantly more frequent, but no significant difference was shown at the variables N0, N1 and N3.

The pT variable shows that significantly less carcinomas were classified as a pT1 in the AMZ as well as a pT3. Besides that, significantly more carcinomas were regarded as in situ, but the variables pT2 and pT4 did not show any difference regarding the national numbers. The pathological classification shows, in contrast to the cN, that not affected lymph nodes (pN0) were classified significantly more frequent in the AMZ and, at the same time, more tumors were N2 and N3.

These TNM classifications lead to the fact that in the AMZ more patients with grade II and grade III tumors were treated and less patients with grade I tumors. In the AMZ, more ductal and mixed tumors were treated compared to the nationwide occurrence of these, but at the same time, less lobular tumors were treated. The mucinous, medullar and tubular types did not show significant difference. Regarding the receptor status, significantly less tumors in the AMZ were ER and PR positive, but, in contrast, less tumors were negatively tested on HER2.

		Patients AMZ (n=602)	**NKR value** (n=47993)	**p-value***
Age at first visit	Mean (SD)	54.41 (10.273)	62.03 (13.732)	0.000
Referred by screening***				
No	%	59	64.3	0.013
Yes	%	41	35.7	
Histological Type				
Ductal	%	82.9	79.59	0.032
Lobular	%	9.5	12.2	0.023
Both lobular and ductal	%	4.5	2.63	0.028
Mucinous	%	1.2	1.85	0.117
Medullar	%	0.5	0.54	0.885
Tubular	%	0.8	0.82	0.977
Other	%	0.7	2.37	-
cT				
Unknown**	%	1.3	2.73	-
No tumor discovered/other**	%	0.2	1.03	-
Carcinoma in situ	%	16.9	1.94	0.000
T1	%	42.4	52.98	0.000
T2	%	30.6	31.47	0.630
T3	%	8.1	5.77	0.034
T4	%	0.5	4.08	0.000
cN				
Unknown**	%	0.2	1.27	-
N0	%	80.7	77.77	0.066
N1	%	15.6	17.98	0.111
N2	%	2.0	0.69	0.023
N3	%	1.5	2.29	0.109
pT				
Unknown**	%	1.7	1.32	-
No tumor discovered/other**	%	5.6	13.42	-
Carcinoma in situ	%	12.8	0.02	0.000
T1	%	54.5	58.24	0.065
T2	%	23.6	23.12	0.787
T3	%	1.8	3.11	0.019
T4**	%	0	0.77	-
pN				
Unknown**	%	3.3	2.76	-
N0	%	74.3	69.17	0.005
N1	%	19.6	22.09	0.125
N2	%	2	3.76	0.002
N3	%	0.8	2.22	0.000
Grade				
Grade I	%	19.8	20.71	0.562
Grade II	%	44.9	39.5	0.009
Grade III	%	26.2	22.13	0.022
Unknown**	%	9.1	17.64	-
ER Status				
Negative	%	13.5	15.05	0.252
Positive	%	73.4	83.17	0.000
Unknown**	%	13.1	1.78	-
PR Status				

*One sample t test is performed, significance is shown
** One sample t test not performed with this value
*** Only one test performed

Negative	%	27.1	30.34	0.072
Positive	%	59.8	65.85	0.003
Unknown**	%	13.1	3.81	-
HER2 Status				
Positive	%	12.5	12.43	0.983
Negative	%	73.9	82.85	0.000
Other**	%	0.3	-	-
Unknown**	%	13.3	4.72	-

Table 9 Tumor characteristics of patients with a primary malignant tumor and operation in the AMZ in comparison with national breast cancer population from 2013-2015

As shown in table 10, significantly less patients had breast-conserving surgery in the AMZ compared to the national breast cancer population. Besides that, if breast-conserving surgery was performed, significantly less patients had neoadjuvant chemotherapy and adjuvant hormonal therapy. Neoadjuvant treatment was given less, but this difference was not significant. The differences in the other (neo-) adjuvant treatment types (in the group of patients who had breast-conserving surgery) appeared not to be significant as well. On the other hand, mastectomies were performed significantly more often. There was no significant difference in the total amount of neoadjuvant treatment prescribed, because neoadjuvant chemotherapy was prescribed significantly more often, but neoadjuvant hormonal therapy significantly less. Considering the adjuvant treatment options, targeted therapy was given significantly more frequent, but hormonal therapy and radiotherapy significantly less frequent.

		AMZ (n=601)	**NKR** (n=50363)	**p-value***
Breast-conserving surgery	**n (% of total n)**	**273 (45.34)**	**30828 (61.21)**	0.000
Neoadjuvant:	% of total n breast-conserving	14.29	18.22	0.065
Only chemotherapy	% of total n breast-conserving surgery	10.62	6.62	0.033
Only hormonal therapy		1.47	1.34	0.864
*Only targeted therapy***		-	2.8	-
*Only radiotherapy***		-	0.14	-
*Chemo- and hormonal***		-	0.27	-
Chemo- and targeted		2.2	2.79	0.506
*Hormonal and targeted***		-	0.07	-
Adjuvant:				
Adj. Chemotherapy	% of total n breast-conserving surgery	20.15	22.11	0.420
Adj. Hormonal therapy		33.7	43.03	0.002
Adj. Targeted therapy		7.34	5.33	0.203
Adj. Radiotherapy		94.14	91.56	0.071
Mastectomy:	**n (% of total n)**	**328 (54.49)**	**19535 (38.72)**	0.000
Neoadjuvant:	% of total n mastectomy	28.96	26.38	0.304
Only chemotherapy	% of total n mastectomy	22.26	16.01	0.007
Only hormonal therapy		0.91	2.18	0.017
*Only targeted therapy***		-	3.76	-
*Only radiotherapy***		-	0.03	-
*Chemo- and hormonal***		-	0.56	-
Chemo- and targeted		5.79	3.72	0.11
*Targeted- and hormonal***		-	0.13	-
Adjuvant:				

Adj. Chemotherapy	% of total n	25.61	25.43	0.941
Adj. Hormonal therapy	mastectomy	42.07	51.16	0.001
Adj. Targeted therapy		13.72	6.9	0.000
Adj. Radiotherapy		20.43	28.43	0.000

Table 10 Treatment options of patients with a primary malignant tumor and operation in the AMZ in comparison with national breast cancer population from 2013-2015

*One sample t test is performed, significance is shown
** One sample t test not performed with this value

5. Discussion

The results of this study indicate that most of the patients lived in the regions Midden-Nederland (665 patients), Den Bosch (414 patients) and Utrecht/Rivierenland (391 patients). Since the AMZ is located in Bilthoven (situated geographically in the middle of the Netherlands) the number of patients in the regions Midden-Nederland and Utrecht/Rivierenland can be explained by the nearby location of the hospital. Even though Den Bosch is still relatively close to the AMZ, the reason for being the 2nd most frequent region is probably not the short distance between this region and the AMZ, but the fact that surgeons and other employees in the hospital worked and lived in that region before working at the AMZ. That is why patients who were treated by those physicians chose to have their follow-up in the AMZ, instead of their hospital in Den Bosch. This resulted in the fact that most follow-up patients came from the region Den Bosch (as shown in figure 3). Besides the regions nearby the hospital, the patients are willing to travel from all regions in the Netherlands to visit the hospital. For example, regions such as Amsterdam, Rotterdam and Oost-Nederland represent a large number of patients in the total population of the AMZ. These results confirm the point of view the Association of Hospitals in the Netherlands (NVZ) stated. The NVZ stated in their report that patients, especially in specialisms such as oncology, are willing to travel long distance for the right care. As an example, about 50% of the patients is willing to travel over an hour longer for a hospital with is associated with higher quality and a better reputation. [39] But, waiting times determine this willingness to travel, which implies that shorter waiting times go hand in hand with more willingness to travel. [39] Since the AMZ is still expecting growth in its number of patients, the question is whether the capacity of the AMZ is large enough to still offer short waiting times during this growth. Longer waiting times due to lack of capacity may influence the number of patients living further away in the future, because longer waiting times may reduce the willingness to travel of the patients living further away.

Considering the type of first contact in relation to the region, it can be seen that the AMZ mostly attracts new patients from the regions Utrecht/Rivierenland and Midden Nederland compared to the regions further away from the AMZ. That means that the number of patients that visit the hospital for a second opinion, is relatively lower in the regions nearby hospital; Utrecht/Rivierenland and Midden Nederland, compared to faraway regions and the results (table 7) have shown that the relation between seeking a second opinion and living in faraway regions was significant. Especially patients from regions such as Limburg, Friesland, Zuidoost Brabant, Breda/Tilburg and Groningen/Drenthe more often initially visit the AMZ to seek a second opinion. These results support the idea of previous research,

which stated that second opinion seekers most likely are residents of non-central metropolitan areas. [40] Besides second opinions, a high percentage of patients with longer travel distance visit the hospital as a new patient as well. The fact that patients from across the country visit the AMZ can be a result of the fact that the term patient engagement has been used increasingly over the past years. There are several definitions of patient engagement, but a well-known definition described patient engagement as the relationship between patients and health care providers as they work together to promote and support active patient and public involvement in health and healthcare and to strengthen their influence on healthcare decisions, at both the individual and collective levels. [41] [42] Patient engagement in practice means that patients are being an "active partner in the care team, setting goals, making decisions and proactively managing his or her health" and besides that the values, experiences and perspectives of the patients are integrated into organizations such as hospitals. The AMZ, as an example of a focus clinic, has implemented these "soft" aspects of care, which could be reasons for patients to be willing to travel longer to receive their care in this specific hospital.

The database of the tumor characteristics consisted of 104 patients in 2013, 208 in 2014 and 290 patients in 2015. As mentioned before, only patients who had a primary diagnosis and had treatment in the AMZ are included in this database. This means that 78%, 50% and 61% in respectively 2013, 2014 and 2015 of the total malign tumor population had a primary diagnosis and had treatment in the AMZ. Partially because of the increasing amount of second opinions over the years 2014 and 2015 (as can be seen in table 1), these percentages of the total malignant tumor population are relatively lower in 2014 and 2015, compared to 2013.

Furthermore, table 1 shows that only 5% of the patients have visited the AMZ for follow-up care. This can be explained by the fact that this research only includes patients who have visited the hospital for the first time in the years 2013-2015. That means that patients who are labeled as patients who came to the AMZ for follow-up care in this research only includes patients that have been diagnosed and treated elsewhere before going to the AMZ. However, it is unclear how many patients have been treated in the AMZ and have received follow-up care in the AMZ as well. This is an important issue for future research, because the AMZ includes many patients with longer travel distance to the hospital, which may influence the willingness of these patients to travel to the AMZ only for follow-up care.

Other results demonstrate that 40-45% of the patients received a benign diagnosis and malignant tumor was diagnosed in 30-35% of the cases. As can be seen in figure 11 in Appendix IV, the diagnosis of the patient changes accordingly to age. Considering the malign and benign tumors, it is shown that most benign tumors are diagnosed in the fertile life phase (15-45) and as the age increases, the number of malign tumors diagnosed increases as well. This confirms previous findings in the literature. [43]

The results of table 5 show that there was no significant relation between the type of first contact and the size of the tumor. However, table 8 in the results section has shown there is a significant relation between second opinion seekers and a higher grade of the tumor (p-value 0.044), which is in accordance to earlier studies. [44] Similarly, there was no significant relation between longer travel distance

(compared to regions nearby the hospital: Utrecht/Rivierenland and Midden-Nederland) and size of the tumor, number of not affected lymph nodes, grade and ER/PR/HER2 status. Nonetheless, it was notable that patients from Friesland and Limburg more often had poorer prognosis regarding their tumors based on cT, cN, grade and ER/PR/HER2 status, but the number of patients coming from these regions was very low (respectively 13 and 18).

Considering the changes over time, the results have shown that the variables referrer, reasons for visiting and grade have shown significant change over the years. However, registration quality of the personal health files differs enormously over the years, which can be accountable to these significant changes over the years. For example, in 2013 28.5% of the referrers were unknown, compared to 58% and 57.5% of the cases in 2014 and 2015. This means that it cannot be concluded that the variable referrer has changed significantly over time, because of this registration quality. Considering the significant change of the reasons patients visited the hospital, change has mostly occurred in the fact that more patients have visited the hospital for a second opinion regarding their diagnosis in 2014 and 2015 compared to 2013. At the same time, this leads to the fact that there has been a decrease in the number of new patients who visit the hospital for suspicion of breast cancer over the years. Looking at the distribution between second opinions regarding diagnosis and second opinions regarding treatment, it was almost equal, which is in agreement with previous research. [28] The tumor characteristics only showed one variable that has changed over the years, namely the differentiation grade. However, analyzing the data without the missing values of this variable shows a p-value of 0.998, which means that the p-value shown in table 3 is declared by the change in the numbers of unknowns. Finally, over the years, significantly less patients had breast-conserving surgery. This could be explained by the fact that the more tumors were classified as pT3 and more patients had grade II and III tumors. The bigger size and higher grade of the tumors over the years could be a reason to choose for a mastectomy instead of breast-conserving surgery. The relation of type of surgery and size and grade of the tumor are shown in table 15 and 16 in Appendix IV.

When looking at the differences of the tumor characteristics of the population of the AMZ with the national breast cancer population, the variables based on the TNM classification show that patients with a relatively better prognosis are treated in the AMZ: more patients with carcinomas in situ and not affected lymph nodes. However, more patients seemed to have a grade II tumor and less patients had tumors with a positive ER and PR status which in their turn leads to poorer prognoses. This leads to the fact that no evident conclusion can be drawn regarding the severity of the tumors of the patients. Besides that, the results have shown that significantly more patients in the AMZ have been detected in the screening program. But, since only women with the age of 50-75 are invited to participate in the screening program and the age of the NKR population is older than the AMZ population, the NKR population may be too old to participate in the screening program and thus cannot be detected during participation in the screening program.

Considering the treatment options in comparison with the national breast cancer population, significantly more patients have had a mastectomy in the AMZ. One of the reasons could be that due to the higher percentage of direct reconstructions, patients are more willing to choose for a mastectomy, because of better cosmetic outcomes. [45] Besides that, in the group of patients with breast-conserving surgery, significantly less patients had neoadjuvant chemotherapy, but in the group of patients with mastectomies, significantly more patients had neoadjuvant chemotherapy. One of the indications for this contradiction could be the age of the patients in both groups: the mean age of patients with breast-conserving surgery was 56.47 compared to an average age of 52.68 in the group of patients with mastectomies (p-value 0.000), because young women seem to have a better response on chemotherapy. [46]. Adjuvant targeted therapy was given significantly more often in the group with mastectomies and the group with breast-conserving surgery also received targeted therapy more frequently as well (however, not significant: p-value is 0.203). This significantly higher amount of targeted therapy was not expected, based on the fact that there was no significant difference with the national breast cancer population regarding positive HER-2 statuses, since targeted therapy is usually prescribed to patients with a positive HER-2 status. [47] Furthermore, adjuvant hormonal therapy was given significantly less frequent in both groups, but this could be explained by the fact that significantly less statuses were ER- and PR positive in the AMZ compared to the national breast cancer population (p-values respectively 0.000 and 0.003).

A striking outcome in this study is that no significant change has been shown regarding the type of first contact of patients in the AMZ. However, it was expected that, at the beginning of the hospital, more patients were follow-ups and 2nd opinions instead of new patients (because of not knowing of the existence of the AMZ) and the years 2014 and 2015 were expected to have relatively more new patients. Nonetheless, table 1 shows that 2013 consisted of more new patients than the years 2014 and 2015. On top of that, over the years, only 5.6%, 4.9% and 5.9% of the patients visited the AMZ to be screened because of (familial) increased risk for developing breast cancer. Over the last year (2016-2017), care for women with genetic predisposition has become an important focus of the hospital, so it would be interesting to see if the number of patients who visit the hospital for this kind of screening has increased during these years.

5.1 Limitations

There have been several limitations that influence the outcomes of this study. First of all, aforementioned, patients with an ASA score of three and higher did not receive any treatment in this hospital, due to the absence of an Intensive Care. This means that the dataset with patients with a primary tumor and who have had surgery in the AMZ cannot include any patients with an ASA score of three and higher. However, the dataset with all patients who had their initial consult in the years 2013-2015 can include patients with an ASA score ≥ 3, since this population also contains patients who only have been diagnosed in the AMZ and did not receive treatment. Since table 9 and table 10 show variables with significant difference compared to the general, nationwide numbers of those variables, change can

be explained by the absence of patients with higher ASA score. Second, the data and analyses of this data show a lot of missing values, both in the dataset derived from the personal health records of the patients of the AMZ and the dataset delivered by the registry. As described earlier in this discussion, these unknown values as a result of fluctuating registration quality have impact on the significant differences of the analyses, which influences the reliability of this study. Lastly, because of the establishment in April of the year 2013, the patient population was relatively smaller compared to 2014 and 2015, which may have effect on the significance of the change over the years.

5.2 Indications for further research

First, the relatively small number of patients in the year 2013 leads to recommendation that further research should exclude this year in the study population and add other years over a longer period of time in order to track changes over time in a more reliable way. Second, looking into the reasons of patients to choose for this hospital as a focus clinic instead of any other general hospital in the Netherlands increases insights in patient characteristics, which are valuable to increase the relevance of this study for marketing purposes. Moreover, insights in the long term clinical effects of patients who have had treatment in the AMZ would be of value, since no previous research has shown long term clinical effects of breast cancer in focus clinics in the Netherlands. Despite the fact that previous research has shown that Dutch patients with ovarian cancer who were treated at a specialized (or semi specialized) hospital had a better survival rate than those treated at a general hospital, a more valuable analysis, based on the AMZ, is still desirable. [27] Fourth, it is remarkable that, the treatment options as mentioned in the results section have shown many significant differences: in the group of patients with breast-conserving surgery less patients had neoadjuvant chemotherapy and adjuvant hormonal therapy, and in the group of patients with a mastectomy more patients had neoadjuvant chemotherapy and adjuvant targeted therapy, but less patient had neoadjuvant hormonal therapy, adjuvant hormonal therapy and adjuvant radiotherapy. The many significant differences of these treatment options with the national policy are not entirely explainable by the data provided in this research, which leads to the recommendation that future research focuses on these treatment options and the indications for these treatment options, for example: size of tumor, reasons of mastectomies or more advanced stages of breast cancer. Lastly, patients visiting the hospital for a second opinion have a large share in the population of the AMZ. Since providing second opinions is an important focus of the hospital, it would be beneficial to examine the outcomes of the second opinion compared to the first opinion regarding both diagnosis and treatment option. Although many studies about discrepancy between second- and first opinions are performed and a previous study about second opinions of breast cancer patients already stated that in 20.3% of the cases the second opinion deviated from the first opinion, it is still of interest to examine this deviation in the unique situation of the AMZ. [22]

6. Conclusion

In conclusion, most new patients lived near the hospital and in Den Bosch, but most second opinions lived further away from the hospital, instead of regions nearby. Among these second opinion seekers, patients are more likely to have a higher grade of the tumor. It has shown that younger patients were more frequently diagnosed with a benign tumor and as the age increased, more malign tumors were diagnosed. Of these malign tumors, the majority was ductal (80-88%) followed by lobular tumors (7-10%). Over the years, more patients have visited the hospital for second opinions compared to new patients or follow-up. This could imply that patients value this specific oriented hospital as a second opportunity to gain more information about their diagnosis and/or treatment. Compared to the national breast cancer population, there was no difference in tumor size. However, more patients in the AMZ had clean lymph nodes, were more frequently diagnosed with a grade II tumor and more often had negative ER and PR receptors. The contradictory differences in these variables lead to the fact that no clear conclusion can be drawn whether the population in the AMZ consisted of less or more severe cases of breast cancer compared to the national breast cancer population. Finally, more patients have received mastectomies instead of breast-conserving surgery in the AMZ. There were contradictory results regarding the treatment options: patients with breast-conserving surgery had significantly less often neoadjuvant chemo therapy and adjuvant hormonal therapy, but patients with mastectomies had significantly more often neoadjuvant chemotherapy and adjuvant targeted therapy. However, within the mastectomy group, significantly less patients had (neo-)adjuvant hormonal therapy and adjuvant radiotherapy.

7. Reflection

Writing this thesis has been very inspiring for me and I feel I have learned a lot during this period. I am very proud of the result, but yet happy to end this period and start a new course in my student life.

Over the past months, changes have occurred in the way of completing my thesis: it turned out I needed more time in the AMZ than I originally thought. Going to Bilthoven 3-4 times per week has been a struggle for me: travel times were long and the work I had to do in the AMZ was tough, because of the many files I had to go through. When I finally thought going through these files got to an end, it turned out the original list was not complete and more files had to be completed. That was when we (me and Joeke Felderhof) decided to exclude one year in the study population. However, reading so many files has given me many more insights in the aspects of breast cancer, which has been very interesting.

The way I put it here, it may seem like I feel like a victim in this situation. But, when reflecting on my own behavior, I should have been more confident to say something when I suspect something is wrong/missing. From the beginning, I had the feeling something in the provided list was missing, but I did not mention this to anyone.

This leads to the next learning moment: during these past months, I had the privilege to work with many professionals (both in the hospital and at the University). Normally, I'm the type of person

who is a leader, thinks critically and is not scared to stand up for her opinion/rights. But in this scenario, I felt a bit overwhelmed by working with these kind of professionals, which affected my critical thinking and standing up for my rights and opinion. This is something I really want to change the next time I write a thesis or start working in a company, to be able to grow as a professional and as a person.

Overall, I have enjoyed completing my thesis the last couple of months and feel like I have learned a lot. Moreover, the result of my thesis has been regarded as very interesting and this have given me the opportunity to convert my thesis into an academic article. I am very grateful the AMZ has given me the trust to do this and I am really looking forward to completing this article.

Nikki Luttikhuis
Enschede, February 2018

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Appendix I

American Society of Anaesthesiologists' (ASA) Physical Status Classification

Table 11. American Society of Anaesthesiologists' (ASA) Physical Status Classification [37]

ASA PS Classification	**Definition**	**Examples, including, but not limited to:**
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

Appendix II

TNM classification

The most common form of staging cancer cases is the TNM classification. The TNM classification is based on three components: the extent of the tumor (T), the absence or presence (and extent) of regional lymph nodes metastasis (N) and the absence or presence of distant metastasis (M). [47] The T-component varies from T0-T4 depending on the size of the tumor. The N-component varies from N0-N3, depending on number of nodes (and size) affected and the M-component is either 0 (no distant metastasis) or 1 (distant metastasis microscopically confirmed). [48] More information is shown in table 1 and 2. In this research, the terms cTNM, which stands for the clinical classification and pTNM, which stands for the pathological classification are used. [49] The TNM classification is used to determine the grade of the tumor, as shown in table 5. More information of the TNM is shown in table 6.

Table 12: Grade Grouping

Grade 0	**T_{is}**	**N_0**	**M_0**
Grade IA	T_1*	N_0	M_0
Grade IB	T_{0-1} *	N_{1mi}	M_0
Grade IIA	T_{0-1}*	N_1	M_0
	T_2	N_0	M_0
Grade IIB	T_2	N_1	M_0
	T_3	N_0	M_0
Grade IIIA	T_{0-2}*	N_2	M_0
	T_3	N_{1-2}	M_0
Grade IIIB	T_4	N_{0-2}	M_0
Grade IIIC	Any T	N_3	M_0
Grade IV	Any T	Any N	M_1

Table 13. Summary of T and N status

T_{is}	**In situ**		
T_1	≤ 2 cm		
T_{1mi}	≤ 0,1 cm		
T_{1a}	> 0,1 cm to 0,5 cm		
T_{1b}	> 0,5 cm to 1,0 cm		
T_{1c}	> 1,0 cm to 2,0 cm		
T_2	> 2 cm to 5 cm		
T_3	> 5 cm		
T_4	Chest wall/skin ulceration, skin nodules, inflammatory		
T_{4a}	Chest wall		
T_{4b}	Skin ulceration, satellite skin nodules, skin oedema		
T_{4c}	Both T_{4a} and T_{4b}		
T_{4d}	Inflammatory carcinoma		
N_1	Movable axillary	pN_{1mi}	Micrometastasis, > 0,2 mm to 2 mm
		pN_{1a}	1-3 axillary nodes
		pN_{1b}	Internal mammary nodes with microscopic/macroscopic metastasis by sen but not clinically detected
		pN_{1c}	1-3 axillary nodes and internal mammary nodes and internal mamm microscopic/macroscopic metastasis by sentinel node biopsy but not clin
N_{2a}	Fixed axillary	pN_{2a}	4-9 axillary nodes

N_{2b}	Internal mammary clinically apparent	pN_{2b}	Internal mammary nodes, clinically detected, without axillary nodes
N_{3a}	Infra-clavicular	pN_{3a}	≥ 10 axillary nodes or infraclavicular
N_{3b}	Internal mammary and axillary	pN_{3b}	Internal mammary nodes, clinically detected, with axillary node(s) or > and internal axillary mammary nodes with microscopic metastasis by sen but not clinically detected
N_{3c}	Supra-clavicular	pN_{3c}	Supra-clavicular

ER/PR status and HER2 status

Molecular classification such as an estrogen (ER) and progesterone (PR) receptors are important in breast cancer research, because of their prognostic and predictive information. [50] Determination of the ER receptor status, for example, predicts the response to endocrine therapy such as tamoxifen. Similarly, determination of the human epidermal growth factor receptor 2 (HER2) helps in selecting targeted therapy against this receptor. The determination of these receptors identified five subtypes of breast cancer: luminal A, luminal B, normal breast-like, HER2-overexpressing and basal-like. The last one, basal-like, is also known as a triple-negative tumor, because these tumors are ER-, PR- and HER2-negative, which is associated with poor prognosis and shorter survival. [51]

Appendix III
Distinction of the regions

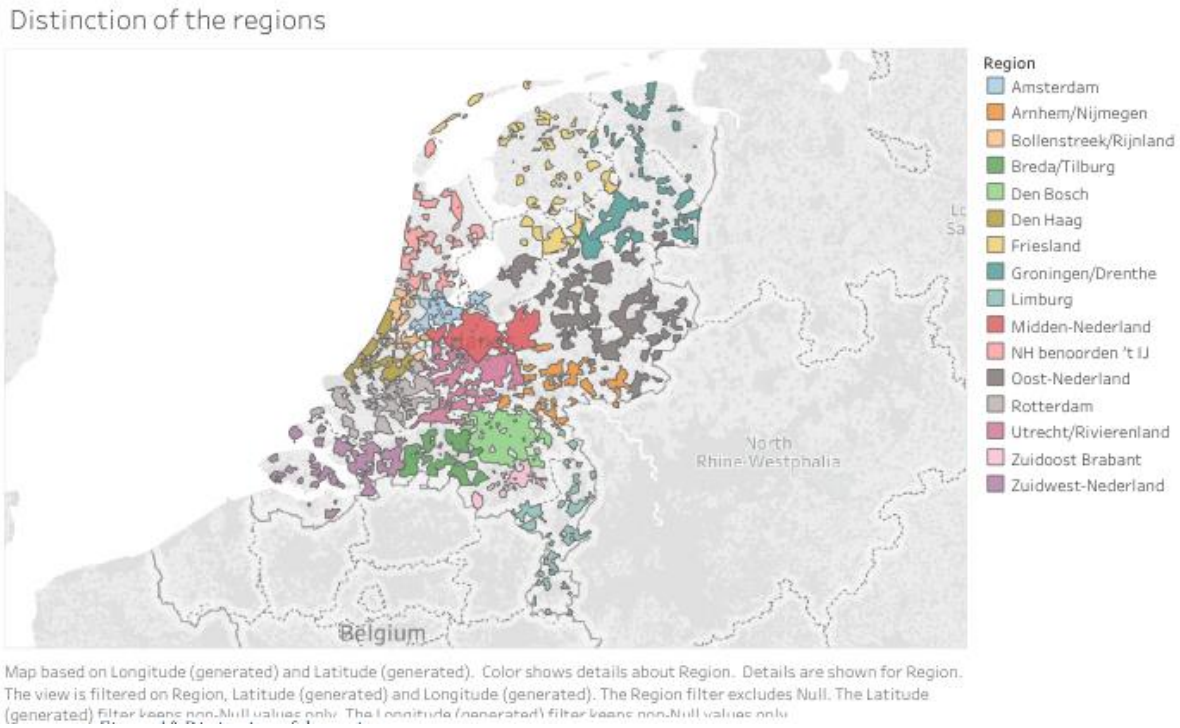

Figure 10 Distinction of the regions

Appendix IV

Additional analyses

Region	**# Triple Negatives**
Arnhem Nijmegen	1
Breda Tilburg	6
Den Bosch	11
Den Haag	4
Friesland	1
Groningen/Drenthe	3
Limburg	4
Midden-Nederland	9
NH benoorden 't IJ	2
Oost-Nederland	5
Rotterdam	2
Utrecht/Rivierenland	2
Zuidwest-Nederland	5

Table 14 Number of triple negatives per region

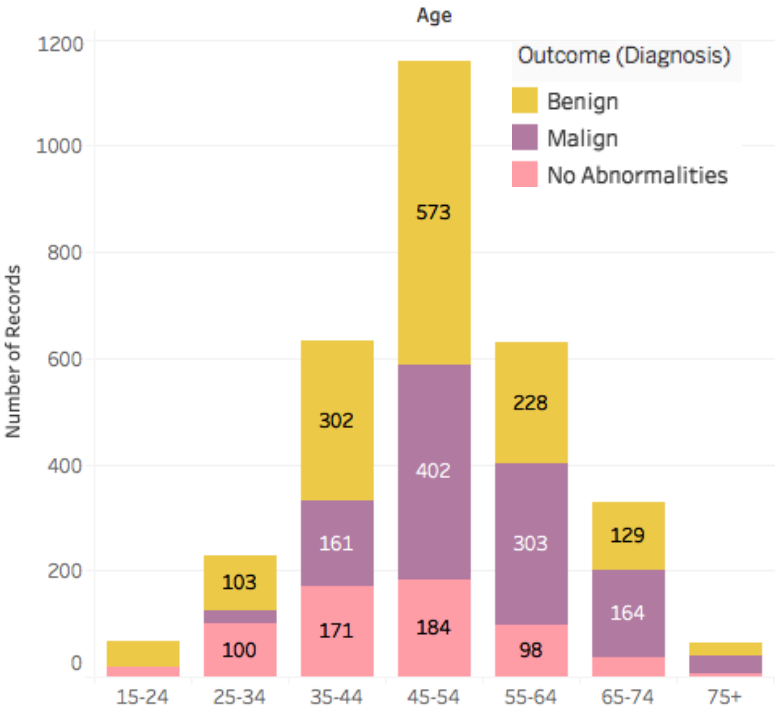

Figure 11 Diagnosis in relation to age of all patients visiting the AMZ from 2013-2015

	Breast-conserving (n=273)	**Mastectomy** (n=328)
pT:		
No tumor discovered	17	17
Carcinoma in situ	37	40
T1	171	156
T2	44	98
T3	0	11
Unknown	4	6

Table 15 Relation between type of operation and size of tumor

	Breast-conserving (n=273)	**Mastectomy** (n=328)
Grade:		
Grade I	69	50
Grade II	122	148
Grade III	68	90
Unknown	14	40

Table 16 Relation between type of operation and grade of tumor