Radiotherapy treatment patterns in the Netherlands

Insights from the Netherlands Cancer Registry

Jelle Evers

RADIOTHERAPY TREATMENT PATTERNS IN THE NETHERLANDS

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GENERAL INTRODUCTION

With an estimated annual number of 19.3-23.5 million new diagnoses worldwide [1,2], cancer stands as one of the largest contributors to the global disease burden [2]. Moreover, the number of cancer diagnoses is increasing, given that most populations are aging and cancer predominantly afflicts the elderly. Specifically in the Netherlands, the number of cancer diagnoses is forecasted to escalate from 118,000 in 2019 to 156,000 in 2032 [3]. This increasing number of people diagnosed with cancer need primary treatment and enroll in aftercare pathways for early detection of recurrent disease, late health effects of cancer treatment and psychosocial support. This poses a challenge for oncological care [6,7], of which future capacity and affordability has been questioned [7]. Prevention of cancer is a key aspect in limiting the upcoming demand of oncological care [8]. Additionally, thoughtful use of the limited health care resources is paramount, underscoring the importance of critically evaluating treatment patterns.

Treatment patterns are determined by treatment decisions. What treatment decision is appropriate differs by patient, because 1) varying treatment strategies proved to be effective across different types and stages of cancer, 2) contextual factors such as patients' age and performance status impact treatment tolerance and outcomes, and 3) patients' preferences regarding treatment (outcomes) are heterogeneous. To illustrate, patients may opt for a particular treatment to pursue curation or prolong survival, while others may prioritize maintaining health-related quality of life and therefore decided upon less intensive or other type of treatment. Also the willingness of risking late health problems related to treatment may differ by patient. Tailoring treatment decision towards the patients' preferences is guided by the process of shared decision making, in which patients actively contribute to treatment decision after being informed by their physician on the possible treatment strategies, expected outcome and late effects.

Treatment guidelines outline eligible treatment strategies based on cancer type and stage, and the availability and level of evidence on treatment outcomes [9,10]. For various types of non-metastatic cancer, guidelines on curative-intent treatment recommend radiotherapy as one of the eligible treatment strategies, either as monotherapy or combined with other treatment modalities like surgery or systemic therapy [11-19]. These types of cancer include, but are not limited to, malignant tumors in the lung, breast, esophagus, prostate, rectum, skin (squamous cell carcinoma, basal cell carcinoma and Merkel cell carcinoma), brain, head and neck area, cervix, and uterus [20-22]. Due to their high incidence

[23] and the (relative) efficacy of radiotherapy, the tumors in the lung, breast, esophagus, prostate and rectum are most often treated at radiotherapeutic facilities. For these tumors, 'optimal' radiotherapy utilization rates (including radiotherapy with palliative-intent, but excluding brachytherapy) have been estimated: 78%, 87%, 74%, 60% and 56%, respectively. These estimations were based on radiotherapy indications in guidelines and the numbers of diagnoses and stage distributions in the Netherlands [21].

Actual radiotherapy utilization rates likely deviate from these 'optimal' estimates, given that it differs by patient what treatment decision is considered appropriate. Furthermore, the eligibility of radiotherapy and therefore actual radiotherapy use continuously changes due to ongoing developments, including *technical developments*, *novel insights in optimal treatment*, and *organizational developments*.

Firstly, the developments of *technical* nature. Early radiotherapy compared to the current standard was more imprecise, leading to a higher radiation dose delivered to the tissue surrounding the target volume, potentially causing significant damage. The localization of the radiotherapy target has since improved; planning treatment using CT-imaging became the standard of care [24,25], and nowadays, MRI-guided radiotherapy is being introduced in various facilities in the Netherlands [25] enabling real-time monitoring of the target. Additionally, both the dose planning and delivery of external beam radiotherapy have improved due to technical innovations in linear accelerators and treatment planning systems, including multi-leaf collimators, intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and advances in radiotherapy approaches such as stereotactic body radiotherapy (SBRT) [24]. In 2018, proton beam radiotherapy became available in the Netherlands [26], allowing for more selective delivery of dose into the target volume and thereby minimizing damage to surrounding tissue, at the aim of limiting side effects [24]. Technical advances have also improved brachytherapy [27] and optimized the use of radiosensitizers [28]. In conclusion, technical advances in radiotherapy continuously limit side effects and optimize effectiveness, leading to new radiotherapy indications. Besides, developments in other treatment modalities also influence the use of radiotherapy. For example, surgery can now be performed robot-assisted, aiming to minimize the risk of surgical complications [29]. This may affect the use of radiotherapy, for example in patients with prostate cancer as surgery and radiotherapy are competing treatment options in many prostate cancer cases.

Secondly, ongoing research continuously generates *novel insights in optimal treatment*. These insights may be derived from or related to other developments, such as technical advances. Research continuously investigates which patients, based on both patient and tumor characteristics, benefit from which (new) treatment approaches. To illustrate, research has shown promising results for SBRT in patients with early non-small cell lung cancer [30-32]. Although surgical resection – and not radiotherapy – has traditionally been the preferred curative treatment strategy in early-stage non-small cell lung cancer, SBRT is nowadays considered an equivalent curative option in selected patients [30-33]. Another example of a novel insight into optimal treatment affecting radiotherapy treatment patterns, not related to technical advances, regards treatment de-escalation in breast cancer. The improvement in breast cancer prognosis [34,35] and novel insights into tailoring treatment towards patients' prognostic risk have allowed for treatment de-escalation in selected patients, aiming to limit side effects while maintaining good treatment results [36]. For instance, studies have successfully identified subgroups of patients with breast cancer in whom radiotherapy following breast conserving surgery can now be omitted [37,38].

Lastly, developments of *organizational* nature. Various efforts have been made in reorganizing oncological care, aimed at increasing the quality of care and decreasing variations throughout the Netherlands [25,39-41]. In the regions, regular multidisciplinary team consultations from multiple hospitals are currently standard practice [39], and structured regional oncology networks meanwhile cover the whole country [40]. These collaborations promote treatment decisions that surpass the expertise available in single hospitals, which is important considering that not all treatment modalities and (new) treatment techniques are (immediately) available in all hospitals. At the national level, oncology specialists with specific expertise have united in professional associations, aiming to promote the quality of their expertise across the country. The radiation oncologists established the Dutch Association of Radiotherapy and Oncology (NVRO), which features tumor-specific working groups. These groups serve as platforms for radiation oncologists with the same tumor-specific specialization to share experience and knowledge (including novel insights from studies), ultimately aiming to acquire nationwide consensus on tumor-specific radiotherapy matters [25,41]. Also, efforts have been made to shift specific (surgical) procedures to limited facilities. This centralization of care increases the volume and subsequently the experience with the

procedures in these few places [42], which is associated with better treatment outcomes [43]. Nevertheless, centralization of care increases travel time for the applicable procedures [42], which possibly raises a barrier to accessibility and affects both the use of the applicable (surgical) procedure and the use of a potential competing treatment strategy. In the availability of external beam radiotherapy, a trend opposed to centralization occurred in the past 15 years: fourteen additional facilities have opened and only one closed, resulting in eighteen radiotherapy institutes currently operating at thirty-four locations (Figure 1). This overall expansion decreased the average one-way travel time for radiotherapy for almost one third of patients, on average by 13 minutes, potentially increasing the accessibility of radiotherapy in the Netherlands.

Figure 1: Radiotherapy locations in the Netherlands providing external beam radiotherapy (in 2023)

Treatment trends over time reflect developments that have led to the current treatment patterns. More specifically, these trends reveal the impact of *technological developments*, *novel insights into optimal treatment*, and *organizational developments* on treatment patterns. Evaluating trends in treatment is not only intriguing but essential; it helps understand current treatment patterns and identify opportunities for optimizing treatment decisions. To illustrate, certain developments (such as the introduction of a new competing treatment modality or treatment de-escalation) may have led to undesired changes in the use of radiotherapy. This can be identified by providing an overview of past trends in radiotherapy use within the broader context of multimodal cancer treatment. Furthermore, a nationwide overview of radiotherapy use could provide insight into treatment variations between patients and hospitals, as well as variations across the country. This insight may also be helpful in identifying opportunities for optimizing treatment decisions, ultimately aiming to optimize the use of limited healthcare resources.

Previously, trends and variations in radiotherapy use for various types of tumors in the Netherlands have been reported until 2008 [44-48]. The NVRO commissioned updated insights into trends in radiotherapy use to assist today's medical specialists – including radiation oncologists in the tumor-specific platforms of the NVRO – in reflecting on current practices and identifying opportunities for further optimizing treatment decisions. This thesis provides an overview and attempts to explain the nationwide trends and variations in the use of primary radiotherapy in non-metastatic stages of four of the most commonly seen cancers at radiotherapeutic facilities: lung cancer – both non-small cell lung cancer (chapter 2) and small cell lung cancer (chapter 3), breast cancer – both ductal carcinoma in-situ (chapter 4) and invasive breast cancer (chapter 5), prostate cancer (chapter 6), and rectal cancer (chapter 7).

In our studies, we utilized data from the Netherlands Cancer Registry from 2008 onwards, with the end of inclusion varying per study. The Netherlands Cancer Registry is a nationwide population-based registry containing information on patient, disease, and treatment of all individuals diagnosed with cancer in the Netherlands since 1989 [49]. The Netherlands Comprehensive Cancer Organisation (IKNL), which hosts the Netherlands Cancer Registry, is notified of newly diagnosed cancers by the Dutch pathology registration (PALGA) and Dutch hospitals, after which trained data managers extract data from the hospitals' medical records. Our studies were limited to primary radiotherapy

and non-metastatic disease because data on treatment of recurrent disease and palliative treatment in metastatic disease were only limitedly available in the Netherlands Cancer Registry. We aimed to gain a comprehensive understanding of the clinical practice reflected by the trends and to focus on insights that might provide opportunities for further optimizing treatment decisions. To that end, radiation oncologists representing the tumor-specific platforms of the NVRO, as well as medical specialists referring for radiotherapy, were involved in our studies. Our ultimate aim was to provide valuable insights contributing to the well-considered use of limited healthcare resources.

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CHAPTER

2

TRENDS AND VARIATIONS IN TREATMENT OF STAGE I-III NON-SMALL CELL LUNG CANCER FROM 2008-2018: A NATIONWIDE POPULATION-BASED STUDY FROM THE NETHERLANDS

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ABSTRACT

Introduction

This Dutch population-based study nationwide treatment patterns and its variations for stage I-III non-small cell lung cancer (NSCLC).

Materials and methods

Patients diagnosed with clinical stage I-III NSCLC in the period 2008-2018 were selected from the Netherlands Cancer Registry. Treatment trends were studied over time and age groups. Use of radiotherapy versus surgery (stage I-II), and concurrent versus sequential chemoradiotherapy (stage III) were analyzed by logistic regression.

Results

In stage I, the rate of surgery decreased from 58% (2008) to 40% (2018) while radiotherapy use increased over time (from 31% to 52%), which mostly concerned stereotactic body radiotherapy (74%). In stage II, 54% of patients received surgery, and use of radiotherapy alone increased from 18% to 25%. The strongest factors favoring radiotherapy over surgery were WHO performance status (OR ≥2 vs 0: 23.39 (95%CI: 18.93-28.90)), increasing age (OR ≥80 vs <60 years: 14.52 (95%CI: 13.02-16.18)) and stage (OR stage II vs I: 0.61 (95%CI: 0.57-0.65)). In stage III, the combined use of chemotherapy and radiotherapy increased from 35% (2008) to 39% (2018). In all years, 23% received concurrent chemoradiotherapy, 9% sequential chemoradiotherapy, 23% radiotherapy or chemotherapy alone, and 25% best supportive care. The strongest factors favoring concurrent over sequential chemoradiotherapy were age (OR ≥80 vs <60 years: 0.14 (95%CI: 0.10-0.19)), WHO Performance status (OR ≥2 vs 0: 0.33 (95%CI: 0.24-0.47)) and region (OR east vs north: 0.39 (95%CI: 0.30-0.50)).

Conclusions

The use of radiotherapy became more prominent over time in stage I NSCLC. Combined use of chemotherapy and radiotherapy marginally increased in stage III: only one third of patients received chemoradiotherapy, mainly concurrently. Treatment variation seen between patient groups suggests tailored treatment decision, while variation between hospitals and regions indicate differences in clinical practice.

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for 80-85% of the lung cancer diagnoses in Western countries [1,2]. Almost one quarter of patients present with stage I, one tenth with stage II and one fifth with stage III disease [3].

Surgery is seen as the preferred treatment modality for stage I-II NSCLC [4-9]. Radiotherapy in general and stereotactic body radiotherapy (SBRT) specifically, however, are alternative curative treatment options for stage I [10,11] and the latter was widely implemented between 2003 and 2008 [12-16]. Around 2010, SBRT was included in international guidelines as an alternative treatment option for inoperable patients with peripheral tumors, but not for those who are considered operable [4-9]. On the other hand, several authors have reported an increasing use of SBRT in early-stage NSCLC, both in operable patients instead of surgery [17] and in patients who previously would have received best supportive care alone [12,15,18].

In patients with unresectable stage III disease, chemoradiotherapy (CRT) has been the standard treatment for more than twenty years [19]. Concurrent CRT (cCRT) is recommended over sequential CRT (sCRT) in international guidelines [7-9], as it decreases locoregional progression and improves overall survival [20]. The recently approved adjuvant treatment with durvalumab further improves outcomes in stage III [21] but is only given to patients with no progression after CRT [9,22]. Although evidence and international guidelines favor cCRT, variation in the use of CRT is seen between and within countries [23-26].

The patterns of care for patients with NSCLC in the Netherlands have been described for earlier years in previous studies [27,28], but a recent elaborative overview also addressing SBRT and detailed CRT options is lacking. Insights into recent patterns of care indicate whether clinical practice meets the treatment guidelines for NSCLC and is furthermore useful for the prediction and planning of future oncological care. This study describes treatment patterns for patients diagnosed with stage I-III NSCLC between 2008 and 2018 in the Netherlands. In addition, variables associated with the use of radiotherapy versus surgery in stage I and II disease, and concurrent versus sCRT in stage III disease were identified. Insights into factors associated with treatment decisions can help to identify patients who received (sub)optimal treatment.

MATERIALS AND METHODS

Patients

Patients diagnosed with clinical stage I-III NSCLC between 2008 and 2018 were selected from the Netherlands Cancer Registry (NCR). The NCR is a nationwide population-based registry containing information on patient, tumor, and the delivered first line treatment of all newly diagnosed cancer patients. Trained registrars extract these data from the Dutch hospitals' medical records. Patients with histologically or cytologically confirmed NSCLC and those with only a clinical diagnosis were included in this study. Patients became only clinically diagnosed in case of a strong suspicion of NSCLC for which treatment was given while histological and cytological confirmation was lacking. Patients who were diagnosed with NSCLC at autopsy, or who resided or received treatment abroad were excluded.

Definitions

Staging was based on the Tumor Node Metastases (TNM) classification edition 6 until 2009, edition 7 in the period 2010-2016, and edition 8 since 2017. Until 2012, 12% of the patients lack TNM and only had Extent of Disease (EoD) available. In brief, EoD describes whether the disease is localized (EoD 2), regionally spread (EoD 3-5) or metastasized (EoD 6). We translated EoD into stages according to the TNM edition applicable for the year of diagnosis. EoD 3 and 4 can be translated into stage II or III, depending on the T- and N-stage. As this information was missing for these records, we randomly assigned stage II or stage III according to the ratio between these stages in 2012-2013 (1:2.7). Alternative approaches to translating EoD were investigated in sensitivity analyses (Supplementary Document 1).

SBRT is a high precision radiotherapy technique that delivers large doses to the tumor in a few fractions. Radiotherapy as part of CRT was always conventionally fractionated. cCRT was defined as chemotherapy and radiotherapy starting within 30 days from each other [23], irrespective of the order. If the end date of therapy was available, radiotherapy starting or stopping during chemotherapy, and chemotherapy starting or stopping during radiotherapy were also considered concurrent, irrespective of the time between the start of both treatment modalities. sCRT was defined as chemotherapy and radiotherapy starting between 30 and 90 days from each other if no part of cCRT. If either chemo- or radiotherapy started with an interval time longer than 90 days and both were not part of CRT, they were classified as distinct treatments. The registration of start and end of therapy was most complete in recent years.

In case chemo- or radiotherapy had a missing start date, the treatment was classified as chemotherapy and radiotherapy not otherwise specified (nos).

We divided the Netherlands into five regions, each including ≥3 radiotherapy institutes and eleven hospitals of which ≥1 university hospital. Driving time to a radiotherapy facility was defined as one way travelling time by car and calculated using the postal code of the nearest radiotherapy facility and the patient's home address. Driving time was clustered by 15 minutes, with a top cluster containing ≥45 minutes driving time.

Hospitals were classified as university or non-university hospitals, where the single cancer specific hospital in the Netherlands was included as university hospital. In addition, the mean annual number of surgeries for NSCLC performed per hospital was calculated and categorized. Since 2012, surgical care for lung cancer in the Netherlands is concentrated in hospitals that perform ≥20 lung cancer resections per year [29]. If a hospital did not perform any surgery for NSCLC in a subset of the years, it was classified in the no surgery-category in these years, and in the applicable category in the other years.

Between 2008 and 2018, half of the radiotherapy institutes provided radiotherapy with curative intent to an annual average of 147 patients or more with stage I-III NSCLC. These institutes were categorized as high volume. The other half of the institutes provided radiotherapy to an annual average of less than 147 patients and were categorized as low volume. Furthermore, radiotherapy institutes were divided by in-house and independent. In-house radiotherapy was defined as a radiotherapy department embedded in the organization of a hospital diagnosing lung cancer, while independent radiotherapy includes radiotherapy institutes not embedded in the organization of a diagnosing hospital.

Comorbidities as registered in the hospitals' medical records were available until 2015 for patients in the southern part of the Netherlands (~15% of the Dutch population, an overview of all comorbidities registered is available in Supplementary Table 1). WHO performance status and reasons for best supportive care were registered nationwide since 2015. WHO performance status, also called ECOG or Zubrod score, is a scale for fitness ranging from experiencing no restrictions in daily activities (score 0) to being completely bedridden (score 4) [30].

Analyses

Patient and disease characteristics as well as the frequency of the various types of treatment modalities were stratified according to stage. Trends in the applied treatment modalities over time and for age groups including five years

were presented in graphs, also stratified for stage. Age groups with less than 30 patients were not shown. For some regions in the earlier years, SBRT might be recorded as conventional radiotherapy in the NCR. Therefore, we decided not present SBRT in the graphs. As the chemotherapy and radiotherapy nos-cohort potentially could include patients treated with CRT, its percentage was added to the lines of cCRT and sCRT and depicted in a dotted format. This was done to estimate the highest possible rate of both cCRT and sCRT.

Logistic regression analyses were performed to identify variables associated with the use of radiotherapy versus surgery in patients with stage I and II, whereby patients receiving both modalities were excluded. As stage II included a limited number of patients and treatment options were comparable to stage I, we combined both stages. To identify variables associated with the use of cCRT versus sCRT in patients with stage III, logistic regression analyses were also used. In these analyses we excluded 2008-2012, as combined modality treatment could then not always be classified due to the missing start and end dates of therapy. Since comorbidities and WHO performance status were only available for subsets of patients, analyses on comorbidities included only those diagnosed in the southern part of the Netherlands until 2015 and analyses on performance status included only those diagnosed in 2015-2018. Analyses were adjusted for all factors that were statistically significant in crude analyses, except for the number of comorbidities and the performance status. Furthermore, all Dutch university hospitals have in-house radiotherapy and frequently perform surgeries for NSCLC, hence the analyses on university versus non-university hospitals were not adjusted for these variables. Ninety-five percent confidence intervals (95%CI) resulting from the analyses reflect probable estimates for the odds radios (OR) using a p-value of 0.05 as critical level.

All analyses were performed using the SAS statistical software, version 9.4, SAS Institute Inc., Cary, NC, USA.

RESULTS

Between 2008 and 2018 a total of 119,789 NSCLC cases were registered, including 61,621 (51%) with clinical stage I-III. The annual number of diagnoses with clinical stage I-III increased from 4,992 in 2008 to 6,580 in 2018 (Supplementary Figure 1). The proportion of stage I remained similar between 2008 (22%) and 2018 (23%), while for stage II the proportion increased from 4% to 9%. For stage III the proportion decreased from 28% to 21%.

Patient characteristics

Fifty-seven percent of the patients with stage I were male, compared to 63% in stage II and III (Table 1). Age distribution and region of residence were comparable across the stages. Of the patients with registered comorbidities, those with stage I more often had ≥1 comorbidity. Chronic pulmonary disease was the most common comorbidity, followed by hypertension and previous malignancies. WHO performance status was available for 26% of patients and those with stage III had the worst performance status. Information on histological type was lacking in 28% of stage I, 13% of stage II and 10% of stage III patients. These patients were registered as having only a clinical diagnosis of NSCLC.

Table 1. Characteristics of patients diagnosed with non-small cell lung cancer in the Netherlands between 2008 and 2018, stratified for clinical stage

	Stage I		Stage II		Stage III	
	N = 25,405		N = 9,272		N = 26,905	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*
Male	14,371	(56.6)	5,875	(63.4)	16,905	(62.8)
Age at diagnosis, years						
<60	4,017	(15.8)	1,462	(15.8)	5,226	(19.4)
60 – 69	8,144	(32.1)	2,801	(30.2)	8,408	(31.3)
70 – 74	4,981	(19.6)	1,753	(18.9)	4,619	(17.2)
75 – 79	4,464	(17.6)	1,619	(17.5)	4,198	(15.6)
≥80	3,799	(15.0)	1,637	(17.7)	4,454	(16.6)
Median (p25, p75)	70.0	(63.0-77.0)	71.0	(63.0-77.0)	69.0	(62.0-77.0)
Period of diagnosis						
2008 – 2010	6,055	(23.8)	1,586	(17.1)	7,576	(28.2)
2011 – 2014	8,521	(33.5)	3,437	(37.1)	9,517	(35.4)
2015 – 2018	10,829	(42.6)	4,249	(45.8)	9,812	(36.5)
Region in the Netherlands						
North	2,704	(10.6)	1,091	(11.8)	3,410	(12.7)
East	4,281	(16.9)	1,674	(18.1)	4,550	(16.9)
South	5,983	(23.6)	2,260	(24.4)	6,674	(24.8)
South west	5,909	(23.3)	2,051	(22.1)	6,067	(22.5)
North west	6,528	(25.7)	2,196	(23.7)	6,204	(23.1)
Morphology						
Squamous cell carcinoma	6,297	(24.8)	3,771	(40.7)	9,721	(36.1)
Adenocarcinoma	10,088	(39.7)	3,243	(35.0)	9,257	(34.4)
Large cell carcinoma	1,660	(6.5)	853	(9.2)	5,114	(19.0)
Clinical diagnosis only	7,093	(27.9)	1,241	(13.4)	2,650	(9.8)
Other	267	(1.1)	164	(1.8)	163	(0.6)

Continued

	Stage I		Stage II		Stage III	
	N = 25,405		N = 9,272		N = 26,905	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*
Primary therapy						
RT alone	10,162	(40.0)	1,872	(20.2)	3,083	(11.5)
Surgery alone	10,283	(40.5)	2,716	(29.3)	1,036	(3.9)
Chemotherapy alone	199	(0.8)	190	(2.0)	3,051	(11.3)
Concurrent CRT	181	(0.7)	464	(5.0)	6,228	(23.1)
Sequential CRT	54	(0.2)	159	(1.7)	2,391	(8.9)
RT and chemotherapy (distinct therapies)	79	(0.3)	84	(0.9)	1,226	(4.6)
RT and chemotherapy, dates unknown	30	(0.1)	68	(0.7)	901	(3.3)
Surgery and chemotherapy	1,578	(6.2)	1,627	(17.5)	856	(3.2)
Surgery and RT	220	(0.9)	216	(2.3)	152	(0.6)
Surgery and RT and chemotherapy (distinct therapies / CRT)	201	(0.8)	424	(4.6)	791	(2.9)
Other/unknown therapy	34	(0.1)	30	(0.3)	365	(1.4)
Best supportive care	2,384	(9.4)	1,422	(15.3)	6,825	(25.4)
Received any RT	10,927	(43.0)	3,287	(35.5)	14,772	(54.9)
Received SBRT	8,082	(74.0)	719	(21.9)	313	(2.1)
Comorbidities at diagnosis being assessed [A]	3,965	(15.6)	1,377	(14.9)	3,989	(14.8)
≥1 comorbidity at diagnosis	3,514	(88.6)	1,125	(81.7)	3,207	(80.4)
Median number of comorbidities (p25, p75)	2.0	(1.0-3.0)	2.0	(1.0-3.0)	2.0	(1.0-3.0)
Most frequent comorbidities						
Chronic pulmonary disease	1,639	(41.3)	477	(34.6)	1,317	(33.0)
Hypertension	1,300	(32.8)	425	(30.9)	1,216	(30.5)
Previous malignancy	1,224	(30.9)	270	(19.6)	622	(15.6)
WHO performance status at diagnosis being assessed [B]	6,886	(27.1)	2,806	(30.3)	6,507	(24.2)
0	3,036	(44.1)	1,223	(43.6)	2,430	(37.3)
1	2,643	(38.4)	1,115	(39.7)	2,619	(40.2)
2	936	(13.6)	325	(11.6)	895	(13.8)
3	247	(3.6)	126	(4.5)	482	(7.4)
4	24	(0.3)	17	(0.6)	81	(1.2)

RT: radiotherapy; CRT chemoradiotherapy; SBRT stereotactic body radiotherapy; p25: 25th percentile; p75: 75th percentile

A   Comorbidities were mainly registered until 2015 and principally for patients in the southern part of the Netherlands

B   WHO performance scores are registered since 2015

Trends in treatment over time

In patients with stage I, the percentage receiving radiotherapy increased from 31% in 2008 to 52% in 2018, whereas the use of surgery decreased (from 58% to 40%) (Figure 1A). Since 2015, more patients received radiotherapy than surgery: 52% and 41%, respectively, in 2015-2018. SBRT was given to 74% of patients with stage I who received radiotherapy. In patients with stage II, surgery remained the most delivered therapy in all years: 54% was operated on in the total study period (Figure 1B). Use of radiotherapy alone in these patients increased from 18% in 2008 to 25% in 2018, while best supportive care decreased. Twenty-two percent of the irradiated patients with stage II received SBRT. In patients with stage III, the use of combined chemotherapy and radiotherapy increased from 35% in 2008 to 39% in 2018 (Figure 1C). In the total study period, 23% of patients received cCRT and 9% sCRT. Eleven percent of the patients with stage III received surgery with or without (neo)adjuvant therapy, 23% radiotherapy or chemotherapy alone, and 25% best supportive care. For all stages, refusal of curative-intent treatment by the patient or family was the main reason for best supportive care.

Trends in treatment according to age

In stage I and II, higher age was associated with less surgery, more radiotherapy, and more best supportive care (Figure 2A and Figure 2B). Radiotherapy use was highest in patients aged 80-84 years. In stage III, higher age was associated with less cCRT and sCRT, more radiotherapy alone and more best supportive care (Figure 2C).

Figure 1. Trends in primary treatment of non-small cell lung cancer in the Netherlands, presented over incidence years and stratified for [A] clinical stage I (N = 25,405), [B] clinical stage II (N = 9,272), [C] clinical stage III (N = 26,905)
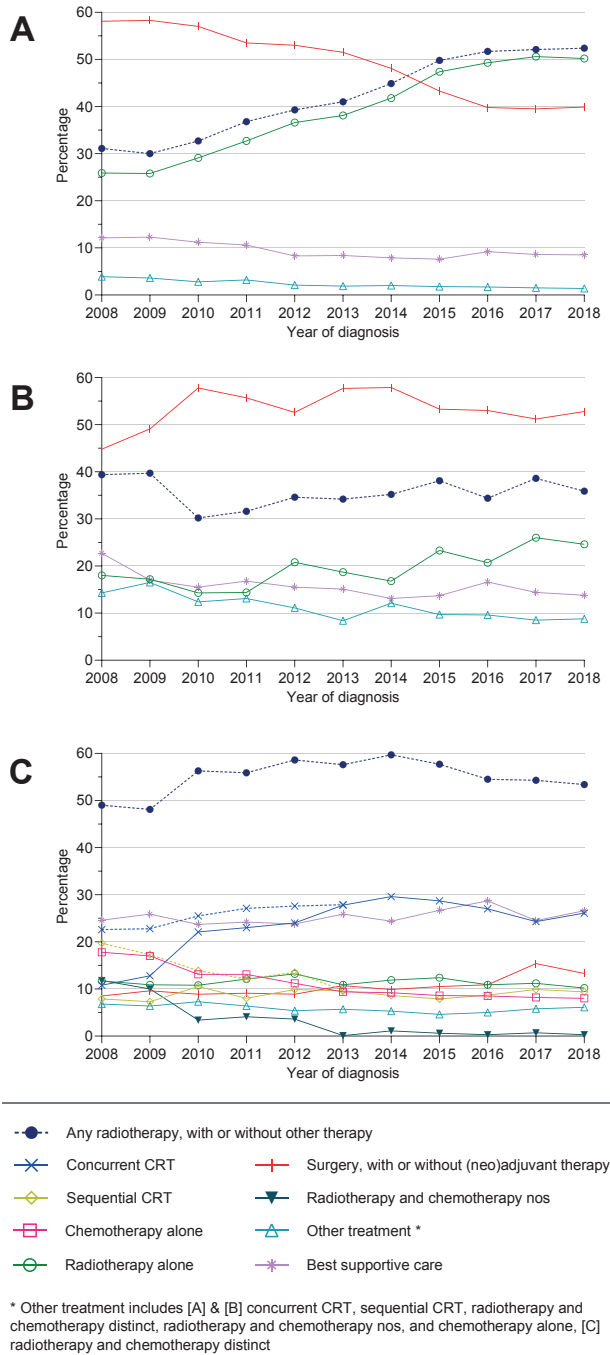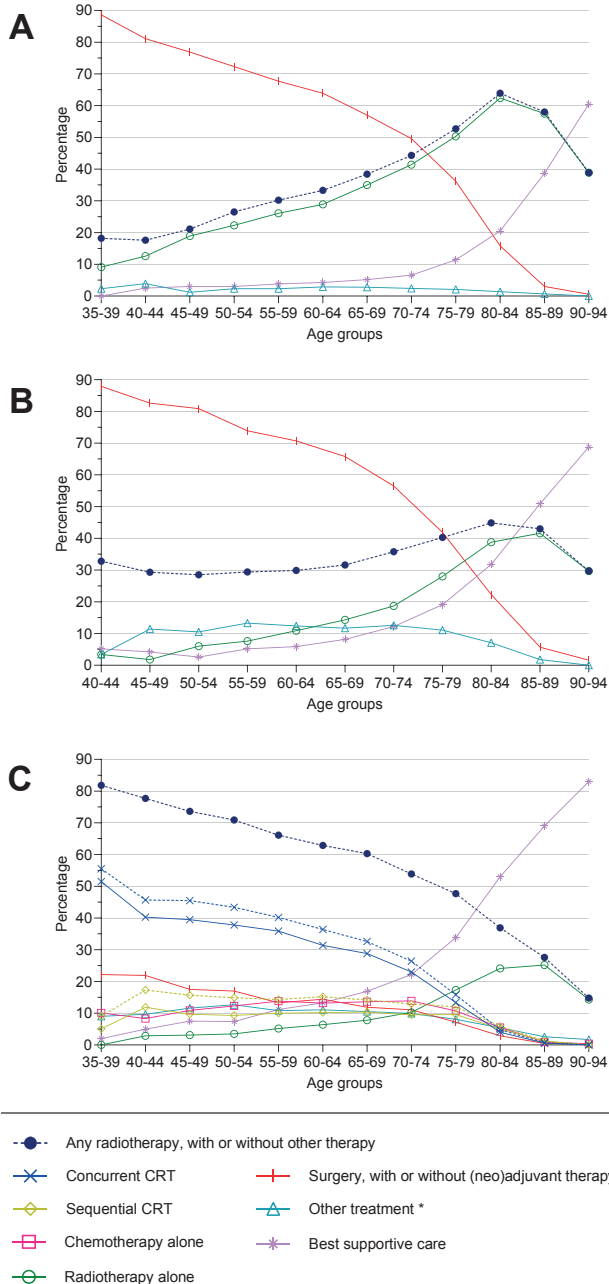
2

Figure 2. Trends in primary treatment of non-small cell lung cancer in the Netherlands, presented according to 5-year age groups and stratified for [A] clinical stage I (N = 25,367), [B] clinical stage II (N = 9,234), [C] clinical stage III (N = 26,852)

Multivariable adjusted analyses: stage I and II

In multivariable analyses, patients with stage I had a higher probability of receiving radiotherapy instead of surgery than those with stage II (Table 2). In addition, female sex and increasing age were associated with increased probability of receiving radiotherapy. ORs ranged from 1.64 (95%CI: 1.52-1.77) in patients aged 60–69 years to 14.52 (95%CI: 13.02-16.18) in those aged ≥80 years, compared to age <60 years. Patients aged ≥70 years (reference: <70 years) had an OR of 3.12 (95%CI: 2.97-3.28) for radiotherapy versus surgery, which was 3.97 (95%CI: 3.75-4.19) in those aged ≥75 years (reference: <75 years). Being diagnosed in more recent years, having more comorbidities and a WHO performance status ≥1 were also associated with a higher probability of receiving radiotherapy.

The likelihood of receiving radiotherapy instead of surgery was lower for patients with a 15-44 minute driving time to a radiotherapy facility, compared to patients with less than 15 minutes driving time. Regional differences in the choice of treatment were evidenced by ORs ranging from 0.85 (95%CI: 0.77-0.93) to 1.17 (95%CI: 1.07-1.28). Patients being diagnosed in a university hospital, in a hospital with no or low volume NSCLC surgery, or with in-house radiotherapy, were more likely to receive radiotherapy. For the latter, the association was the strongest (OR: 1.57, 95%CI: 1.46-1.69). The association of in-house radiotherapy with treatment remained fairly constant over time and differences between regions were present in the whole study period (Supplementary Table 2). Non-university hospitals, however, were only associated with less use of radiotherapy in 2015-2018.

Table 2. Odds ratios (OR) of receiving radiotherapy (RT) compared to surgery for patients diagnosed with clinical stage I-II non-small cell lung cancer in the Netherlands between 2008 and 2018

	RT		Surgery		Crude		Adjusted [A]	
	N = 13,153		N = 16,204					
	n	*(%)*	*n*	*(%)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*
Stage								
I	10,506	(79.9)	11,861	(73.2)	Reference		Reference	
II	2,647	(20.1)	4,343	(26.8)	**0.69**	**(0.65-0.73)**	**0.61**	**(0.57-0.65)**
Sex								
Male	7,770	(59.1)	9,209	(56.8)	Reference		Reference	
Female	5,383	(40.9)	6,995	(43.2)	**0.91**	**(0.87-0.96)**	**1.08**	**(1.03-1.14)**
Age at diagnosis, years [B]								
<60	1,213	(9.2)	3,682	(22.7)	Reference		Reference	
60 – 69	3,396	(25.8)	6,368	(39.3)	**1.62**	**(1.50-1.75)**	**1.64**	**(1.52-1.77)**
70 – 74	2,648	(20.1)	3,278	(20.2)	**2.45**	**(2.26-2.66)**	**2.51**	**(2.31-2.73)**
75 – 79	2,892	(22.0)	2,182	(13.5)	**4.02**	**(3.69-4.38)**	**4.31**	**(3.94-4.71)**
≥80	3,004	(22.8)	694	(4.3)	**13.14**	**(11.83-14.59)**	**14.52**	**(13.02-16.18)**
Period of diagnosis								
2008 – 2010	2,172	(16.5)	4,050	(25.0)	Reference		Reference	
2011 – 2014	4,215	(32.0)	5,898	(36.4)	**1.33**	**(1.25-1.42)**	**1.36**	**(1.27-1.46)**
2015 – 2018	6,766	(51.4)	6,256	(38.6)	**2.02**	**(1.89-2.15)**	**2.09**	**(1.94-2.24)**
Region in the Netherlands								
North	1,523	(11.6)	1,734	(10.7)	Reference		Reference	
East	2,067	(15.7)	2,886	(17.8)	**0.82**	**(0.75-0.89)**	**0.88**	**(0.80-0.97)**
South	2,783	(21.2)	4,208	(26.0)	**0.75**	**(0.69-0.82)**	**0.85**	**(0.77-0.93)**
South west	3,044	(23.1)	3,536	(21.8)	0.98	(0.90-1.07)	0.92	(0.84-1.01)
North west	3,736	(28.4)	3,840	(23.7)	**1.11**	**(1.02-1.20)**	**1.17**	**(1.07-1.28)**
One way driving time for radiotherapy, minutes								
<15 minutes	5,373	(40.8)	5,984	(36.9)	Reference		Reference	
15 - <30 minutes	6,491	(49.3)	8,288	(51.1)	**0.87**	**(0.83-0.92)**	**0.91**	**(0.86-0.96)**
30 - <45 minutes	1,178	(9.0)	1,781	(11.0)	**0.74**	**(0.68-0.80)**	**0.86**	**(0.78-0.95)**
≥45 minutes	111	(0.8)	151	(0.9)	0.82	(0.64-1.05)	1.06	(0.80-1.39)
Median (p25, p75)	17.0	(10.0-23.0)	18.0	(11.0-24.0)	**0.99** [C]	**(0.99-0.99)**	1.00 [C]	(0.99-1.00)
Type of institute of diagnosis								
University	1,702	(12.9)	1,892	(11.7)	Reference		Reference	
Non-university	11,450	(87.1)	14,307	(88.3)	**0.89**	**(0.83-0.95)**	**0.85**	**(0.79-0.92)**
In-house radiotherapy in the institute of diagnosis								
No	9,550	(72.6)	12,655	(78.1)	Reference		Reference	
Yes	3,602	(27.4)	3,544	(21.9)	**1.35**	**(1.28-1.42)**	**1.57**	**(1.46-1.69)**

Continued

	RT		Surgery		Crude		Adjusted [A]	
	N = 13,153		N = 16,204					
	n	(%)	n	(%)	OR	(95%CI)	OR	(95%CI)
The average annual number of surgeries for NSCLC in the institute of diagnosis								
≥20	9,598	(73.0)	12,361	(76.3)	Reference		Reference	
10 – <20	484	(3.7)	794	(4.9)	**0.79**	**(0.70-0.88)**	1.04	(0.92-1.19)
1 – <10	379	(2.9)	501	(3.1)	0.97	(0.85-1.12)	**1.26**	**(1.08-1.47)**
No surgery	2,691	(20.5)	2,543	(15.7)	**1.36**	**(1.28-1.45)**	**1.41**	**(1.32-1.52)**
Number of comorbidities [D]								
0	135	(7.3)	476	(18.1)	Reference		Reference	
1	451	(24.2)	821	(31.2)	**1.94**	**(1.55-2.42)**	**1.93**	**(1.52-2.45)**
2	517	(27.8)	665	(25.3)	**2.74**	**(2.19-3.43)**	**2.47**	**(1.94-3.15)**
≥3	757	(40.7)	669	(25.4)	**3.99**	**(3.21-4.96)**	**3.41**	**(2.69-4.33)**
Median (p25, p75)	2.0	(1.0-3.0)	2.0	(1.0-3.0)	**1.39** [C]	**(1.33-1.46)**	**1.34** [C]	**(1.27-1.40)**
WHO performance status [E]								
0	1,165	(26.3)	2,773	(66.3)	Reference		Reference	
1	2,080	(46.9)	1,291	(30.9)	**3.83**	**(3.48-4.23)**	**3.79**	**(3.40-4.21)**
≥2	1,192	(26.9)	118	(2.8)	**24.04**	**(19.66-29.40)**	**23.39**	**(18.93-28.90)**

RT: radiotherapy; OR: odds ratio; CI: confidence interval; p25: 25th percentile; p75: 75th percentile; values in bold are statistically significant

A   The analyses were corrected for clinical stage, sex, age at diagnosis, period of diagnosis, region, one way driving time for radiotherapy, type of institute of diagnosis, whether the institute of diagnosis had in-house radiotherapy, and the average annual number of surgeries for NSCLC in the institute of diagnosis. The analyses on the type of institute of diagnosis is not corrected for in-house radiotherapy and the average annual number of surgeries for NSCLC. WHO performance status and comorbidities were only included in the multivariable models on these variables

B   Crude and adjusted ORs are 3.03 (95%CI: 2.89-3.18) and 3.12 (95%CI: 2.97-3.28), respectively, for patients aged ≥70 years compared to those aged <70 years, and 3.76 (95%CI: 3.57-3.97) and 3.97 (95%CI: 3.75-4.19), respectively, for patients aged ≥75 years compared to those aged <75 years

C   Variable included as continuous factor, with value 0 as reference

D   Analyses in a subset of patients diagnosed until 2015 in the southern part of the Netherlands

E   Analyses in a subset of patients diagnosed since 2015

Multivariable adjusted analyses: stage III

In patients diagnosed with stage III disease in the period 2013-2018, female sex (OR: 0.82, 95%CI: 0.72-0.94) and higher age were associated with a lower probability to be treated with cCRT instead of sCRT (Table 3). The OR for cCRT versus sCRT was 0.22 (95%CI: 0.16-0.29) in patients aged ≥70 versus <70 years and 0.25 (95%CI: 0.18-0.34) in those aged ≥75 versus <75 years. No association

between the number of comorbidities and treatment was present. Patients with a WHO performance status ≥1 were less likely to receive cCRT than those with a performance status of 0.

Table 3. Odds ratios (OR) of receiving concurrent chemoradiotherapy (CRT) compared to sequential CRT for patients diagnosed with clinical stage III non-small cell lung cancer between 2013 and 2018

	Concurrent CRT		Sequential CRT		Crude		Adjusted [A]	
	N = 3,968		N = 1,319					
	n	*(%)*	*n*	*(%)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*
Sex								
Male	2,318	(58.4)	757	(57.4)	Reference		Reference	
Female	1,650	(41.6)	562	(42.6)	0.96	(0.85-1.09)	**0.82**	**(0.72-0.94)**
Age at diagnosis, years [B]								
<60	1,181	(29.8)	232	1,181	Reference		Reference	
60 – 69	1,608	(40.5)	489	1,608	**0.65**	**(0.54-0.77)**	**0.64**	**(0.54-0.76)**
70 – 74	727	(18.3)	253	727	**0.56**	**(0.46-0.69)**	**0.56**	**(0.46-0.69)**
75 – 79	372	(9.4)	232	372	**0.31**	**(0.25-0.39)**	**0.30**	**(0.24-0.37)**
≥80	80	(2.0)	113	80	**0.14**	**(0.10-0.19)**	**0.14**	**(0.10-0.19)**
Period of diagnosis								
2013 – 2015	2,051	(51.7)	624	(47.3)	Reference		Reference	
2016 – 2018	1,917	(48.3)	695	(52.7)	**0.84**	**(0.74-0.95)**	**0.87**	**(0.77-0.99)**
Region in the Netherlands								
North	618	(15.6)	115	(8.7)	Reference		Reference	
East	550	(13.9)	254	(19.3)	**0.40**	**(0.31-0.52)**	**0.39**	**(0.30-0.50)**
South	1,019	(25.7)	303	(23.0)	**0.63**	**(0.49-0.79)**	**0.62**	**(0.48-0.79)**
South west	811	(20.4)	314	(23.8)	**0.48**	**(0.38-0.61)**	**0.44**	**(0.35-0.56)**
North west	970	(24.4)	333	(25.2)	**0.54**	**(0.43-0.69)**	**0.50**	**(0.40-0.64)**
One way driving time for radiotherapy, minutes								
<15 minutes	1,575	(39.7)	520	(39.4)	Reference		Reference	
15 - <30 minutes	2,056	(51.8)	665	(50.4)	1.02	(0.89-1.17)	1.02	(0.89-1.17)
30 - <45 minutes	318	(8.0)	122	(9.2)	0.86	(0.68-1.08)	0.85	(0.67-1.09)
≥45 minutes	19	(0.5)	12	(0.9)	0.52	(0.25-1.08)	0.54	(0.25-1.17)
Median (p25, p75)	17.0	(11.0-23.0)	17.0	(11.0-23.0)	1.00 [C]	(0.99-1.00)	1.00 [C]	(0.99-1.00)
Type of institute of diagnosis								
University	405	(10.2)	87	(6.6)	Reference		Reference	
Non-university	3,563	(89.8)	1,232	(93.4)	**0.62**	**(0.49-0.79)**	**0.65**	**(0.51-0.84)**
Radiotherapy institute volume of NSCLC treatments								
Low volume	1,213	(30.6)	370	(28.1)	Reference		Reference	
High volume	2,751	(69.4)	949	(71.9)	0.88	(0.77-1.01)	0.87	(0.75-1.01)

Continued

	Concurrent CRT		Sequential CRT		Crude		Adjusted [A]	
	N = 3,968		N = 1,319					
	n	(%)	n	(%)	OR	(95%CI)	OR	(95%CI)
Number of comorbidities [D]								
0	124	(24.3)	27	(19.1)	Reference		Reference	
1	158	(31.0)	47	(33.3)	0.73	(0.43-1.24)	0.82	(0.47-1.42)
2	116	(22.7)	32	(22.7)	0.79	(0.45-1.40)	0.88	(0.48-1.60)
≥3	112	(22.0)	35	(24.8)	0.70	(0.40-1.22)	0.85	(0.46-1.56)
Median (p25, p75)	1.0	(1.0-2.0)	1.0	(1.0-2.0)	0.90 [C]	(0.78-1.04)	0.94 [C]	(0.80-1.09)
WHO performance status [E]								
0	1,012	(51.5)	236	(34.9)	Reference		Reference	
1	849	(43.2)	358	(53.0)	**0.55**	**(0.46-0.67)**	**0.62**	**(0.51-0.75)**
≥2	103	(5.2)	82	(12.1)	**0.29**	**(0.21-0.40)**	**0.33**	**(0.24-0.47)**

CRT: chemoradiotherapy; OR: odds ratio; CI: confidence interval; p25: 25th percentile; p75: 75th percentile; values in bold are statistically significant

A   The analyses were corrected for age at diagnosis, period of diagnosis, region, and type of institute of diagnosis. WHO performance status and comorbidities were only included in the multivariable models on these variables

B   Crude and adjusted ORs are 0.51 (95%CI: 0.45-0.58) and 0.22 (95%CI: 0.16-0.29), respectively, for patients aged ≥70 years compared to those aged <70 years, and 0.36 (95%CI: 0.31-0.42) and 0.25 (95%CI: 0.18-0.34), respectively, for patients aged ≥75 years compared to those aged <75 years

C   Variable included as continuous factor, with value 0 as reference

D   Analyses in a subset of patients diagnosed until 2015 in the southern part of the Netherlands

E   Analyses in a subset of patients diagnosed since 2015

The use of either cCRT or sCRT differed by region, with ORs ranging from 0.39 (95%CI: 0.30-0.50) to 0.62 (95%CI: 0.48-0.79). Furthermore, patients diagnosed in a non-university hospital had a lower probability of receiving cCRT than those diagnosed in a university hospital (OR: 0.65, 95%CI: 0.51-0.84). No association between driving time to a radiotherapy facility and the delivered CRT schedule could be found. The difference between university and non-university hospitals was comparable over time, while regional differences decreased over time (Supplementary Table 3).

DISCUSSION

This nationwide study demonstrates an increased use of radiotherapy instead of surgery in patients with stage I NSCLC in the Netherlands over the past decade. In stage II, the rate of radiotherapy as sole therapy slightly increased over time, while the rate of best supportive care decreased. Use of combined chemotherapy and radiotherapy marginally increased in stage III. Only one third of these patients received CRT, about two thirds of whom concurrently. Treatment varied between patients, hospitals, and regions.

Stage I and II

The strong increasing trend in radiotherapy use in stage I disease differs from the trend reported earlier in the Netherlands. Between 1990 and 2009, a slight increase in radiotherapy use was seen in a nationwide study [28] and another study including four Dutch regions showed no change in the use of radiotherapy in stage I and II in 1997-2008 [27]. This might be explained by SBRT being not widely available at that time, however information on the percentage of patients receiving SBRT lacked in these studies. For the period 2008-2018, we showed in nationwide data that most irradiated patients with stage I received SBRT (74%), which possibly is an underestimation as SBRT might be reported as conventional radiotherapy in the NCR in some regions in the earlier years.

The finding of increased use of radiotherapy instead of surgery is in line with treatment trends observed in early-stage NSCLC in the USA [17], and may reflect the consideration of SBRT being also a valuable alternative treatment option in operable patients or patients refusing surgery. Although the guidelines for the treatment of NSCLC only recommend SBRT in inoperable patients [7-9], a pooled analysis of clinical trials suggested equipoise for overall survival between SBRT and surgery in operable patients [10]. Observational studies, however, showed a better overall survival after surgery [16,31-34], although these studies may be subject to unmeasured and consequently unadjusted selection bias, as a result of patient selection or physician preferences for surgery or SBRT [35,36].

Studies from the Netherlands and Australia comparing the periods before and after the clinical introduction of SBRT, showed a shift from palliative radiotherapy/best supportive care to curative radiotherapy [12,15,18]. Our study included the period after the implementation of SBRT in the Netherlands (2005-

2007 [12,15]) and demonstrated that the decreasing trend of best supportive care slightly continued in stage I. In stage II, a change in treatment from best supportive care to the use of radiotherapy was demonstrated. However, this shift depends on the translation from EoD to TNM (Supplementary Document 1). Furthermore, the use of different editions of TNM affected our results in patients with stage II, as tumors sized 5-7 cm (T2bN0) were considered stage I in edition 6 and stage II in edition 7. Tumors of 5 cm or larger are not ideal candidates for SBRT [7-9], hence patients with these tumors probably received surgery, which may explain the 9% increase in surgery in stage II between 2009 and 2010. Most other changes in TNM editions are within stages and therefore do not significantly affect our results.

A recently published Dutch study showed that patients were more frequently selected for radiotherapy instead of surgery when they were older and had a lower clinical T stage [37]. In addition, the current study found that female sex, comorbidities, and a WHO performance status ≥1 were patient characteristics associated with increased likelihood of receiving radiotherapy compared to surgery. Also in studies from other countries patients were less likely to receive surgery with a WHO performance status ≥1 [24,34], comorbidities [17,24], or at higher age [17,24], suggesting uniform tailoring of treatment to these patients. Males and females, however, had equal probability of receiving surgery compared to no-surgery [24] or radiotherapy [17,34] in these studies. Reasons for treatment differences between gender in the Netherlands remain unknown.

Although the Netherlands is a small country and the distance to health care facilities is relatively short, we demonstrated differences between regions and clusters of driving time in the choice of treatment. Regional differences in the use of radiotherapy were previously reported for the period 1997-2008 in the Netherlands [27]. Increased travel time was associated with less surgery in England, although 10-minute clusters of driving time were not associated with radiotherapy use [38]. We showed that a 15-44 minute driving time to a radiotherapy facility was associated with less radiotherapy and more surgery compared to less than 15 minutes driving time. The probability of receiving radiotherapy in patients with ≥45 minutes driving time, however, did not differ from those in the <15 minute-cluster. This may be explained by the opportunity of patients with considerable travel time to stay near the hospital during the treatment period [39,40].

We demonstrated a higher probability of radiotherapy use in patients diagnosed in a university hospital, in hospitals with in-house radiotherapy or with no or less than 10 surgeries for NSCLC per year. These observations suggest that treatment decisions in the Netherlands rely upon expertise available in the hospital where NSCLC is initially diagnosed. Contrary to our findings, the use of radiotherapy or surgery did not differ between university and non-university hospitals in the USA. Treatment decision in the USA, however, was associated with health care insurance status [17], which is irrelevant in the Netherlands as all residents have a compulsory basic health care insurance package covering both surgery and radiotherapy [41].

Stage III

The benefit of combined treatment with chemotherapy and radiotherapy in patients with unresectable stage III NSCLC became apparent more than 20 years ago [19]. As a consequence, the combined use of chemotherapy and radiotherapy in patients with stage III in the Netherlands strongly increased in 1990-2009. No information on CRT schedules was reported [28]. The current study shows that the increase in the combined use of chemotherapy and radiotherapy slightly continued between 2008 and 2018. However, only one third of the patients received CRT, most (72%) concurrently. Other patients with stage III received radiotherapy (12%) or chemotherapy (11%) alone, surgery (11%) or best supportive care (25%). Comorbidities, performance status, tumor size and patient's decision are indicated to be the prime reasons for non-radical intent treatment in stage III in one Dutch regional cancer care network [42]. The rates of CRT in Belgium and South Korea are comparable to our results [23,24,26]. However, sCRT was more frequently administered in Belgium [23] and half of the South Korean patients treated with CRT received trimodality treatment (including surgery) [26], which was given to only 3% of all stage III patients in our study. In the USA, CRT is more frequently used and the proportion of definitive CRT given concurrently is almost 85% [25].

Previously, it was reported that female and older patients were more likely to receive sCRT instead of cCRT than male and younger patients in the Netherlands [23], which was also shown in the current study for the years 2013-2018. Reasons behind the treatment difference in males and females should be explored in future research. In the USA and Belgium, CRT use diminished with increasing age [24,25], but no association between age and treatment schedule

was observed [23,25]. Patients with a WHO performance status of 0 or 1 are considered eligible for cCRT [43], and no tailoring of CRT treatment is expected for performance status 1 compared to 0. However, in this study, patients with a WHO performance status 1 were less likely to receive chemoradiation concurrently. In Belgium, though, no difference in CRT schedule was found between patients with a performance status of 0 and 1 [24].

We furthermore showed heterogeneity in the application of cCRT in clinical practice in the Netherlands, which may be unwarranted. A higher probability of treatment with cCRT was demonstrated in the northern part of the Netherlands, which is considered rural compared to other regions. No associations were found between driving time and cCRT versus sCRT. In the USA, metropolitan regions did not differ from non-metropolitan regions in the probability of receiving CRT instead of radiotherapy alone, while increased distance to a care facility was modestly associated with a higher probability of CRT use [25]. Patients in the current study were more likely to receive cCRT instead of sCRT when they were diagnosed in a university hospital. In Belgium and the USA, however, the type of hospital of diagnosis did not affect the probability of receiving CRT [24,25].

Considerations

This study provides insights into variation of treatment between patients, hospitals and regions, indicating which patients received (sub)optimal treatment. Part of the treatment variation seen between patient groups suggests tailored treatment decision, although not all variation may be based on outcomes or shared decision making. Moreover, the variation reported between hospitals and regions indicate differences in clinical practice. Our findings were discussed in the Dutch Association of Radiation Oncology's division of lung cancer and all radiotherapy institutes were provided the opportunity to receive feedback on the distribution of treatment in the region of their institute. The distribution of treatment in regions of the other institutes were shown as benchmark, as well as the overall distribution in the Netherlands. In a future study, this variation may be related to survival and potentially patient reported outcomes to determine best practices.

Invasive procedures to obtain a histological or cytological confirmation may pose a significant risk of complications in fragile patients. Therefore, these procedures may be omitted in patients with clinical suspicion of NSCLC who

are not fit enough to undergo these procedures [15,44]. In this study, 28% of clinical stage I cases lack histological or cytological confirmation, most of whom received radiotherapy. Only 9% lacked confirmation in a study in the USA [45]. Previously, the probability of malignancy was calculated to be 90% in patients in the Netherlands with clinical stage I who received SBRT [46]. Therefore, it is unlikely that we included a substantial number of patients with benign disease.

Observational studies applied various age criteria for defining elderly [12,15,25,27,28,32,34]. When using the arbitrary age criterion ≥70 compared to ≥75 years, elderly with stage I or II had a different probability of receiving radiotherapy versus surgery, while the probability of receiving cCRT versus sCRT in elderly with stage III was comparable. However, we showed a gradual shift in treatment across ages instead of a strict age limit above which treatment choice differed, also in stage III. Our findings imply that instead of the calendar age the biological age is used as criterion for treatment selection, which is in line with guidelines on the treatment of NSCLC stating that treatment decision should reflect the fitness of individual patients rather than age [7,8].

Around 2012-2014, multiple radiotherapy facilities in the Netherlands opened satellite departments, resulting in a reduction of the mean driving time to a radiotherapy facility from 20.6 minutes in 2008 to 16.9 minutes in 2018. Due to the observational nature of our study, we cannot say if this development changed treatment patterns significantly.

Strengths and limitations

Comorbidities and WHO performance status were only available for a subset of patients, hampering detailed analyses. Another limitation is that we have only information on delivered but not intended treatment. As a result of progression before starting radiation in intended sCRT, only chemotherapy may be delivered. Consequently, the number of sCRT treatments actually delivered is likely less than the number of intended sCRT treatments. Furthermore, reasons for non-compliance to the treatment guidelines are not registered, except for reasons for best supportive care. Another limitation was that stratification of stage IIIa and IIIb was impeded by the different TNM editions applicable in the study period, in which subgrouping of stage IIIa and IIIb changed and an additional category (IIIc) was introduced (TNM8). Finally, the use of adjuvant treatment

with durvalumab after CRT in stage III disease could not be evaluated, as durvalumab was introduced only in 2018. Nevertheless, this population-based study provides a comprehensive overview of the developments and variations in treatment for stage I-III NSCLC in the Netherlands between 2008 and 2018.

Conclusions

This nationwide population-based study demonstrates patterns of care in stage I-III NSCLC in the Netherlands during the recent period 2008-2018. Radiotherapy is the predominant treatment modality in stage I since 2015, whereas surgery remained the most frequently applied therapy in stage II. The combined use of chemotherapy and radiotherapy only marginally increased in stage III. In 2018, only 26% of patients with stage III received cCRT. In all stages, treatment varied between patient groups which suggests tailored treatment. Treatment variation between hospitals and regions indicate differences in clinical practices.

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Supplementary document 1: Sensitivity analyses on the translation of EoD

Until 2012, no TNM was available if pathological confirmation was lacking. Only Extent of Disease (EoD) was registered. The following table describes the definition of different EoD stages.

EoD	Definition	Note
1	In situ	Should not be included in our study
2	Localized	
3	Regional: by direct extension	
4	Regional: to lymph nodes	
5	Regional: both by direct extension and to lymph nodes	
6	Distant metastasis	Should not be included in our study

For 12% of patients diagnosed between 2008 and 2011, the diagnosis was not pathologically confirmation. The distribution of these patients over the years and over EoD stages are presented below. EoD stages 1 and 6 are not listed, as these should be translated into Tis and stage IV disease, respectively, which should not be included in our study.

| Year	EoD	N
2008	2	372
	3	29
	4	133
	5	24
2009	2	419
	3	33
	4	153
	5	30
2010	2	404
	3	35
	4	152
	5	41
2011	2	525
	3	30
	4	170
	5	45

EoD 2 can be translated into T1-2 N0 M0, which is stage I in TNM 6 and 7. In TNM 7, an EoD 2 tumor >7 cm would be T3; T3 N0 M0 is stage II in TNM 7. Tumor size is unknown for these patients. To compare the two possibilities for translation, the trends in treatment over time were presented for patients with stage I and II, once while translating all EoD 2 into stage I and once while translating EoD 2 into stage I in the TNM 6 years (2008-2009) and into stage II in the TNM 7 years (2010-2011). The figures in which EoD 2 is translated into stage I in all years, best fit the trends of treatment over the years, as presented below. We therefore decided to translate EoD 2 in all years (2008-2011) into stage I.

Translating all EoD 2 into stage I
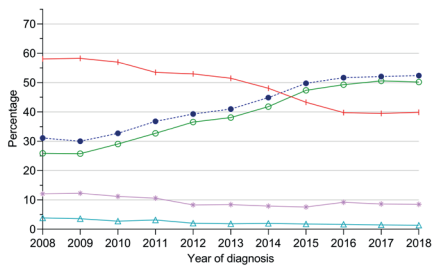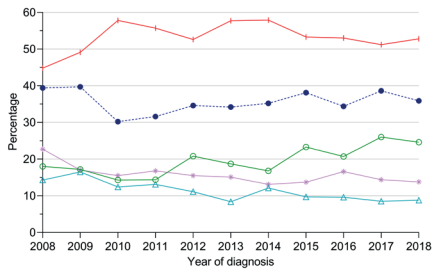
Trends in primary treatment of clinical **stage I** non-small cell lung cancer

Translating EoD 2 into stage I in 2008-2009 and into stage II in 2010-2011

Trends in primary treatment of clinical **stage I** non-small cell lung cancer
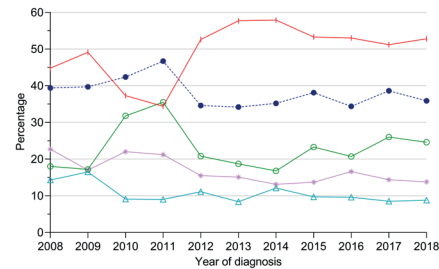
Trends in primary treatment of clinical **stage II** non-small cell lung cancer

Trends in primary treatment of clinical **stage II** non-small cell lung cancer

Legend:
- ──+── Surgery, with or without (neo)adjuvant therapy
- ──●── Any radiotherapy, with or without other therapy
- ──○── Radiotherapy alone
- ──△── Other treatment *
- ──✳── Best supportive care

* Other treatment includes concurrent CRT, sequential CRT, radiotherapy and chemotherapy distinct, radiotherapy and chemotherapy nos, and chemotherapy alone

In case there is no mediastinal involvement, EoD 3 can be translated into T3 N0 M0 which is stage II in TNM 6 and 7. In case of mediastinal involvement, EoD 3 should be translated into T4 N0 M0, which is stage III in TNM 6 and 7. Information on mediastinal involvement are lacking for these patients.

EoD 4 can be translated into either T1-2 N1 M0 (which is stage II in TNM 6 and 7) and T1-2 N2-3 M0 (which is stage III in TNM 6 and 7), depending on the involved lymph nodes. Which lymph nodes are involved is unknown.

Translating all EoD 3 and 4 into stage II

Trends in primary treatment of clinical **stage II** non-small cell lung cancer

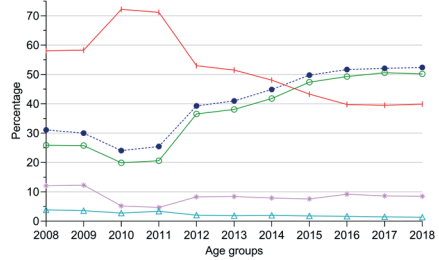**Translating all EoD 3 and 4 into stage III**

Trends in primary treatment of clinical **stage II** non-small cell lung cancer

Trends in primary treatment of clinical **stage III** non-small cell lung cancer

Trends in primary treatment of clinical **stage III** non-small cell lung cancer

Legend:
- Any radiotherapy, with or without other therapy
- Concurrent CRT
- Sequential CRT
- Chemotherapy alone
- Radiotherapy alone
- Surgery, with or without (neo)adjuvant therapy
- Radiotherapy and chemotherapy nos
- Other treatment *
- Best supportive care

* Other treatment includes [stage II graphs] concurrent CRT, sequential CRT, radiotherapy and chemotherapy distinct, radiotherapy and chemotherapy nos, and chemotherapy alone, [stage III graphs] radiotherapy and chemotherapy distinct

To assess the best translation for EoD 3 and 4, sensitivity analyses were performed. First, we translated all EoD 3 and 4 into stage II, and presented the trends of therapies over time for stage II and III. Then we translated all EoD 3 and 4 into stage III, and presented the therapies over time stratified for the stages. Resulting figures are presented below.

For both translations, the trends in therapies seem reasonable. It is probable that the group of patients with EoD 3 and 4 in fact are a highly mixed group of patients with stage II and III. We therefore decided to randomize the EoD 3 and 4 patients between stage II and III, according the ratio of stage II and III in the years 2012-2013. The ratio of stage II and III in these years is: 0.372 (1,767 / 4,742). The figures in the paper are the result of this randomization and the trends in these figures are an intermediate of the trends in the figures above.

EoD 5 should be translated into T3-4 N1-3 M0, which is stage III in both TNM 6 and 7.
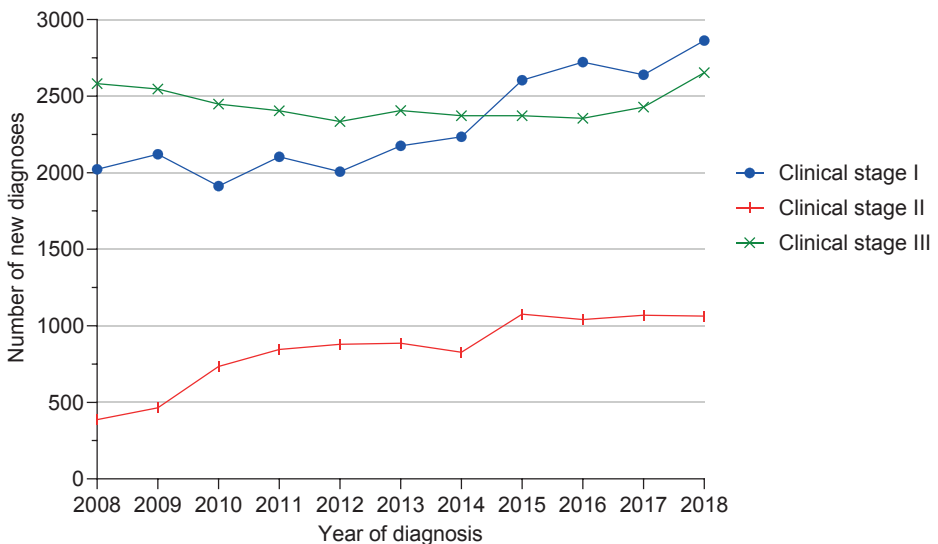
Supplementary Figure 1. Trends in the number of new diagnoses of clinical stage I-III non-small cell lung cancer in the Netherlands, presented over incidence years

Supplementary Table 1. All comorbidities registered in the Netherlands Cancer Registry

arrhythmia
aneurysm aorta (abdominal / thorax)
angina pectoris (ap)
arterial disease nos
atrial fibrillation or flutter
autoimmune hemolytic anemia
cardiomyopathy
carotid artery stenosis
cerebrovascular accident (cva)
cerebrovascular disease nos
choledocholithiasis
chronic glomerulonephritis or pyelonephritis
chronic pulmonary disease: chronic obstructive pulmonary disease, chronic bronchitis
connective tissue disorder nos
coronary artery disease nos
decompensation cordis
deep vein thrombosis
dementia, Alzheimer's disease
diabetes mellitus
disorders of the muscles, connective tissue or joints nos
diverticulitis
hemiparesis, quadriplegia or paraplegia
hemophilia
hepato-biliary diseases, including cirrhosis, hepatitis, liver failure
HIV positive
hypercholesterolemia
hypertension
hypo- / hyperthyroidism
immune thrombocytopenic purpura
inflammatory bowel disease
intermittent claudication
kidney diseases or kidney failure
malaria
multiple sclerosis
myocardial infarct
other neuromuscular disorders
other relevant comorbidities
pancreatitis
parkinsonism
Parkinson's disease
peptic ulcer disease
peripheral arterial disease
previous malignancies
psoriasis
psychiatric disorder
pulmonary disorders nos
pulmonary embolism
pulmonary fibrosis
rheumatoid arthritis (ra), lupus erythematosus, or scleroderma
sarcoidosis
thrombosis nos

Continued

| transient ischemic attack, reversible ischemic neurologic deficit, or amaurosis fugax |
| tuberculosis |
| valvular heart disease |
| vascular disease nos |
| vasculitis, granulomatosis with polyangiitis, or polyarteritis nodosa |
| vitamin B12 deficiency anemia |

nos: not otherwise specified

Supplementary Table 2. Adjusted [A] odds ratios (OR) of receiving radiotherapy compared to surgery for patients diagnosed with clinical stage I-II non-small cell lung cancer in the Netherlands, stratified for periods of time

	2008-2010		2011-2014		2015-2018	
	OR	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*
Region in the Netherlands						
North	Reference		Reference		Reference	
East	0.98	(0.78-1.23)	0.93	(0.79-1.11)	**0.81**	**(0.70-0.94)**
South	**1.35**	**(1.09-1.66)**	**0.81**	**(0.69-0.95)**	**0.70**	**(0.61-0.80)**
South west	0.95	(0.77-1.18)	0.86	(0.73-1.01)	0.93	(0.81-1.07)
North west	1.17	(0.95-1.44)	1.15	(0.98-1.35)	**1.18**	**(1.03-1.35)**
Type of institute of diagnosis						
University	Reference		Reference		Reference	
Non-university	1.01	(0.84-1.21)	0.89	(0.77-1.02)	**0.79**	**(0.71-0.88)**
In-house radiotherapy in the institute of diagnosis						
No	Reference		Reference		Reference	
Yes	**1.73**	**(1.46-2.03)**	**1.49**	**(1.31-1.69)**	**1.58**	**(1.41-1.77)**

OR: odds ratio; CI: confidence interval; values in bold are statistically significant

A   The analyses were corrected for clinical stage, sex, age at diagnosis, period of diagnosis, region, one way driving time for radiotherapy, type of institute of diagnosis, whether the institute of diagnosis had in-house radiotherapy, and the average annual number of surgeries for NSCLC in the institute of diagnosis. The analyses on the type of institute of diagnosis is not corrected for in-house radiotherapy and the average annual number of surgeries for NSCLC

Supplementary Table 3. Adjusted [A] odds ratios (OR) of receiving concurrent chemoradiotherapy (CRT) compared to sequential CRT for patients diagnosed with clinical stage III non-small cell lung cancer in the Netherlands, stratified for periods of time

	2013-2015		2016-2018	
	OR	*(95%CI)*	*OR*	*(95%CI)*
Region in the Netherlands				
North	Reference		Reference	
East	**0.30**	**(0.20-0.43)**	**0.50**	**(0.35-0.71)**
South	**0.61**	**(0.42-0.87)**	**0.62**	**(0.45-0.87)**
South west	**0.37**	**(0.25-0.52)**	**0.53**	**(0.38-0.73)**
North west	**0.40**	**(0.28-0.57)**	**0.62**	**(0.44-0.86)**
Type of institute of diagnosis				
University	Reference		Reference	
Non-university	**0.62**	**(0.44-0.88)**	**0.69**	**(0.48-0.97)**

OR: odds ratio; CI: confidence interval; values in bold are statistically significant

A   The analyses were corrected for age at diagnosis, period of diagnosis, region, and type of institute of diagnosis

CHAPTER

3

Total radiotherapy in stage I SCLC

TRENDS AND VARIATIONS IN THE TREATMENT OF STAGE I-III SMALL CELL LUNG CANCER FROM 2008 TO 2019: A NATIONWIDE POPULATION-BASED STUDY FROM THE NETHERLANDS

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ABSTRACT

Objectives:

Recent treatment patterns for small cell lung cancer (SCLC) in the Netherlands were unknown. This nationwide population-based study describes trends and variations in the treatment of stage I-III SCLC in the Netherlands over the period 2008-2019.

Materials and methods:

Patients were selected from the population-based Netherlands Cancer Registry. Treatments were studied stratified for clinical stage. In stage II-III, factors associated with the use of concurrent (cCRT) versus sequential chemoradiation (sCRT) and accelerated versus conventionally fractionated radiotherapy in the context of cCRT were identified.

Results:

In stage I (N=535), 29% of the patients underwent surgery in 2008-2009 which increased to 44% in 2018-2019. Combined use of chemotherapy and radiotherapy decreased in stage I from 47% to 15%, remained constant (64%) in stage II (N=472), and increased from 57% (2008) to 70% (2019) in stage III (N=5,571). Use of cCRT versus sCRT in stage II-III increased over time (odds ratio (OR) $_{2008-2011 \text{ vs } 2016-2019}$: 0.53 (95%-confidence interval (95%CI): 0.41-0.69)) and was strongly associated with lower age, WHO performance status 0, and diagnosis in a hospital with in-house radiotherapy. Forty-six percent of patients with stage III received cCRT in 2019. Until 2012, concurrent radiotherapy was mainly conventionally fractionated, thereafter a hyperfractionated accelerated scheme was administered more frequently (57%). Accelerated radiotherapy was strongly associated with geographic region (OR$_{\text{south vs north}}$: 4.13 (95%CI: 3.00-5.70)), WHO performance (OR$_{1 \text{ vs } 0}$: 0.50 (95%CI: 0.35-0.71)), and radiotherapy facilities treating ≥16 vs <16 SCLC patients annually (OR: 3.01 (95%CI: 2.38-3.79)).

Conclusions:

The use of surgery increased in stage I. In stages II and III, the use of cCRT versus sCRT increased over time, and since 2012 most radiotherapy in cCRT was accelerated. Treatment regimens and radiotherapy fractionation schemes varied between patient groups, regions and hospitals. Possible unwarranted treatment variation should be countered.

INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 12% of all lung cancer diagnoses worldwide and is often (~70%) metastasized at first presentation [1]. Almost all patients without distant metastases are diagnosed with locoregionally advanced disease [2]. Historically, SCLC was classified either as limited (disease confined to one hemithorax and regional lymph nodes that can be encompassed in the same radiation portal as the primary tumor) or extensive disease (the remainder). Limited disease roughly translates into the potentially curable TNM stages I-III, whereas extensive disease translates into stage IV [3].

Chemoradiation (CRT) is the cornerstone of treatment with curative intent for non-metastatic SCLC since the 1980s [4,5]. However, for very early stages (T1-2N0), surgical resection and stereotactic body radiotherapy (SBRT), both followed by adjuvant chemotherapy, are considered valid treatment strategies [6-8]. For advanced non-metastatic disease stages, concurrent CRT (cCRT) is the standard of care. Sequential CRT (sCRT) is used in unfit patients [6-8]. In 1999, a randomized phase III-trial showed that an accelerated twice-daily radiotherapy fractionation scheme was more effective than the conventional once-daily scheme [9]. However, concerns about its toxicity and logistic issues have challenged the adaptation of the twice-daily scheme [10,11]. In patients in good clinical condition who have no progressive disease after CRT, prophylactic cranial irradiation (PCI) is recommended [12]. Nevertheless, PCI results in a significant neurocognitive decline [13] and did become controversial as in stage IV disease, when compared to only MRI follow-up of the brain, survival was not superior after PCI and MRI follow-up, despite a reduced incidence of brain metastases [14].

Patterns of care for PCI in the Netherlands have previously been described [15]. This study describes further recent trends in treatment strategies for stage I-III SCLC in the Netherlands (2008-2019), which remained unclear. Furthermore, variables associated with the use of cCRT versus sCRT and accelerated versus conventionally fractionated radiotherapy in the context of cCRT were identified. These data provide insights into the variations in curative treatment regimens applied in SCLC from 2008 until 2019.

MATERIALS AND METHODS

Study population

Patients diagnosed with clinical stage I-III SCLC in 2008-2019 were selected from the nationwide Netherlands Cancer Registry (NCR), which contains information on patient, disease, and the primary treatment given [16]. Trained data managers extracted these data from hospitals' medical records. TNM editions 6 (2008-2009), 7 (2010-2016), and 8 (2017-2019) were used. Patients diagnosed at autopsy, or who resided or received treatment abroad were excluded.

Definitions

Combined use of radiotherapy and chemotherapy was classified as cCRT, sCRT or distinct therapies (Supplementary Figure 1). Concurrent treatment was defined as either chemotherapy or radiotherapy starting during the other treatment modality, or the modalities starting ≤30 days from each other. Sequential treatment was defined as chemotherapy and radiotherapy staring 31-≤90 days apart. If the interval between the start of chemotherapy and radiotherapy was longer than 90 days, the modalities were classified as distinct treatments. In case of a missing starting date, treatments were classified as chemotherapy and radiotherapy not otherwise specified (nos). Both PCI and SBRT combined with chemotherapy were classified as distinct therapies. Radiotherapy in the context of cCRT was considered accelerated when the interval between the start and end of a full course of radiotherapy was 15-28 days. A radiotherapy course less than 15 days or exceeding 28 days was considered terminated prematurely and conventionally fractionated, respectively.

We divided the Netherlands into five geographic regions, each including ≥3 radiotherapy facilities and ≥11 hospitals, including ≥1 university hospital. Clustered travelling times to a radiotherapy facility, defined as a one-way trip by car, were: <15, 15–<30 or ≥30 minutes. Radiotherapy facilities' volume was dichotomized: half of the facilities provided radiotherapy to a mean of <16 patients with stage I-III SCLC annually, the other half to a mean of ≥16 patients. Furthermore, radiotherapy facilities were divided by in-house (embedded in the organization of a diagnosing hospital) and independent (other facilities).

Data on comorbidities at diagnosis as registered in medical records were available only until 2015 for patients in the southern part of the Netherlands

(covering ~15% of the Netherlands) [17]. WHO performance status, also referred to as ECOG or Zubrod scale [18], and reasons for best supportive care (BSC) were registered for all patients since 2015.

Analyses

Patient and disease characteristics, the frequency of applied combined treatment modalities, and trends in treatment over time as well as for separate age groups were all stratified for clinical stage. Because of the limited number of patients with stage I and II, trends in these stages were not statistically tested and the graphs on these stages present moving averages over three subsequent years and age groups. For stage III disease the trends in treatment over time were tested using a univariable linear regression analyses. As patients within the chemotherapy and radiotherapy nos-cohort potentially received CRT, this percentage was added to the lines of both cCRT and sCRT and depicted in a dotted format to represent an estimate of their highest possible rates.

In patients with stage II and III disease, logistic regression analyses were performed to identify variables associated with the use of cCRT versus sCRT and accelerated versus conventionally fractionated cCRT. As stage II included a limited number of patients and because the received treatments were largely comparable to those of stage III, both stages were combined. In stage I, the treatment applied differs, but the small number of patients hampered further investigation in treatment variation. For each association investigated, a set of variables for adjustment were selected. Variables were included in the adjustment set if including the variable in multivariable analyses changed one of the odds ratios (OR) of the association investigated with at least 10% compared to the ORs resulting from the univariable analyses. The number of comorbidities and WHO performance status were never included in the adjustment sets, as these variables were only limited available. The analyses on university versus non-university hospitals were furthermore never adjusted for in-house radiotherapy, as this is considered a basic component of university hospitals. Ninety-five percent confidence intervals (95%CI) reflect probable estimates for the OR using a p-value of 0.05 as critical level.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, USA)

RESULTS

Patient characteristics

A total of 20,678 patients were diagnosed with SCLC in 2008-2019. The proportion of stage IV disease increased from 64% in 2008 to 70% in 2019, while the proportion of stage III disease decreased from 32% to 24%. The proportions of stage I (3%) and stage II disease (1-3%) remained constant. This study includes 6,578 (32%) patients diagnosed with clinical stage I-III disease. One patient was excluded from our study because of treatment abroad.

Almost half of the patients were male and the median ages at diagnosis in stage I, II and III disease were 70, 69 and 67 years, respectively (Table 1). In patients for whom comorbidities were assessed, 80-88% had at least one comorbidity, of which hypertension was most prevalent. Seventeen percent of stage I patients had a WHO performance status ≥2, whereas these figures were 20% and 22% for stage II and III cases, respectively. Surgery was the treatment mostly applied in stage I (received by 35%), followed by cCRT (18%) and radiotherapy alone (17%). In stage II and III, cCRT was most often applied (42% and 39%, respectively), followed by surgery in stage II (18%) and chemotherapy alone in stage III (19%). Nine percent of patients with stage I and II disease received BSC, which was 14% of those with stage III disease. Refusal of curative-intent treatment by the patient was the main reason.

Table 1. Characteristics of patients in the Netherlands diagnosed with small cell lung cancer in 2008-2019, stratified for clinical stage

	Stage I		Stage II		Stage III	
	N = 535		N = 472		N = 5,571	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*
Male	278	(52.0)	237	(50.2)	2,643	(47.4)
Age at diagnosis, years						
<60	75	(14.0)	79	(16.7)	1,212	(21.8)
60 – <70	185	(34.6)	174	(36.9)	2,088	(37.5)
70 – <75	111	(20.7)	98	(20.8)	962	(17.3)
75 – <80	89	(16.6)	78	(16.5)	781	(14.0)
≥80	75	(14.0)	43	(9.1)	528	(9.5)
Median (p25, p75)	70.0	(63.0, 77.0)	69.0	(61.0, 75.0)	67.0	(61.0, 74.0)
Period of diagnosis						
2008 – 2011	180	(33.6)	144	(30.5)	2,006	(36.0)
2012 – 2015	177	(33.1)	149	(31.6)	1,881	(33.8)
2016 – 2019	178	(33.3)	179	(37.9)	1,684	(30.2)

Continued

| | Stage I | | Stage II | | Stage III | |
| | N = 535 | | N = 472 | | N = 5,571 | |
	n	*(%)*	*n*	*(%)*	*n*	*(%)*
Region						
North	53	(9.9)	61	(12.9)	760	(13.6)
East	99	(18.5)	84	(17.8)	997	(17.9)
South	135	(25.2)	141	(29.9)	1,406	(25.2)
South west	116	(21.7)	70	(14.8)	1,175	(21.1)
North west	132	(24.7)	116	(24.6)	1,233	(22.1)
Comorbidities at diagnosis being assessed [A]	85	(15.9)	74	(15.7)	835	(15.0)
≥1 comorbidity at diagnosis	68	(80.0)	65	(87.8)	671	(80.4)
Median number of comorbidities (p25, p75)	2.0	(1.0, 3.0)	2.0	(1.0, 3.0)	1.0	(1.0, 3.0)
Most frequent comorbidities						
Hypertension	21	(24.7)	25	(33.8)	282	(33.8)
Chronic pulmonary disease	32	(37.6)	29	(39.2)	256	(30.7)
Diabetes mellitus	14	(16.5)	9	(12.2)	141	(16.9)
WHO performance status at diagnosis available [B]	152	(28.4)	161	(34.1)	1,523	(27.3)
0	68	(44.7)	54	(33.5)	491	(32.2)
1	58	(38.2)	75	(46.6)	695	(45.6)
2	21	(13.8)	24	(14.9)	240	(15.8)
3	5	(3.3)	7	(4.3)	77	(5.1)
4	0	(0.0)	1	(0.6)	20	(1.3)
Primary therapy						
Concurrent CRT	94	(17.6)	200	(42.4)	2,165	(38.9)
Sequential CRT	12	(2.2)	16	(3.4)	421	(7.6)
RT and chemotherapy - distinct therapies	40	(7.5)	56	(11.9)	770	(13.8)
RT and chemotherapy - nos	23	(4.3)	11	(2.3)	223	(4.0)
RT alone	92	(17.2)	26	(5.5)	109	(2.0)
Chemotherapy alone	36	(6.7)	35	(7.4)	1,065	(19.1)
Surgery (+/- chemotherapy, +/- RT)	189	(35.3)	85	(18.0)	41	(0.7)
BSC / other therapy / unknown therapy [C]	49	(9.2)	43	(9.1)	777	(13.9)
Received any RT (excl. PCI)	269	(50.3)	328	(69.5)	3,703	(66.5)
Received SBRT	82	(30.5)	13	(4.0)	15	(0.4)
Received PCI	168	(31.4)	243	(51.5)	2,774	(49.8)

CRT: chemoradiation; RT: radiotherapy; BSC: best supportive care; SBRT: stereotactic body radiotherapy; PCI: prophylactic cranial irradiation; p25: 25th percentile; p75: 75th percentile

A   Comorbidities were registered until 2015 for patients in the southern part of the Netherlands

B   WHO performance status is registered since 2015 and missing for 34.9% of the patients diagnosed in 2015-2019

C   13 patients (all with clinical stage III) received other/unknown therapy

Trends in treatment

In stage I, the percentage of patients treated with both chemotherapy and radiotherapy decreased from 47% in 2008-2009 to 15% in 2018-2019, while the use of surgery increased from 29% to 44% (Figure 1). Seventy-one percent of these patients received adjuvant chemotherapy. Fifty-six percent of those undergoing surgery in 2008-2013 had no prior pathology confirmation, which decreased to 39% in 2014-2019. The percentage of patients receiving radiotherapy alone increased from 8% in 2008-2009 to 22% in 2018-2019, of whom 75% received SBRT. Only 16% of patients receiving SBRT had also chemotherapy administered.

In stage II, the rate of combined use of chemotherapy and radiotherapy remained constant over time (64%) (Figure 2). In 2008-2009, some combined use could not be classified due to a missing start date. Since 2010, 44% of the patients received cCRT, 3% sCRT and 12% chemotherapy and radiotherapy as distinct therapies. The proportion of concurrently treated patients receiving accelerated radiotherapy increased from 24% (2009-2011) to 65% (2018-2019). Only a subset of stage II patients underwent surgery (18%) or received SBRT (4%).

In stage III, the percentage of patients receiving both chemotherapy and radiotherapy increased from 57% in 2008 to 70% in 2019 (p<0.001) (Figure 3). Four percent of patients had treatment classified as chemotherapy and radiotherapy nos, mainly in 2008-2009. The use of cCRT increased from 37% in 2010 to 46% in 2019 (p<0.001), while use of sCRT (8%) and use of the modalities as distinct therapies remained constant in 2010-2019 (15%) (p=0.97 and p=0.30, respectively). Since 2012, most patients treated with cCRT received accelerated radiotherapy (57%). The use of chemotherapy alone decreased from 28% (2008) to 14% (2019) (p<0.001).

In patients with stage I disease, 39% received PCI in 2008-2009, 46% in 2011-2013 and 13% in 2018-2019. These figures were 46-50%, 55-59% and 40-41% in patients with stage II and III disease, respectively.

In all stages, treatment shifted gradually across ages (Supplementary Figure 2). Older patients received less often surgery, cCRT and PCI, and more often radiotherapy alone or BSC. In stage II and III, older patients also received more often chemotherapy without radiotherapy.

Clinical stage I

Figure 1. Trends over the years of diagnosis for [A] all primary treatment applied (%) and [B] use of both chemotherapy and radiotherapy (%), in patients with clinical stage I small cell lung cancer in the Netherlands, N = 535 (moving averages over 3 subsequent years)

Clinical stage II

Figure 2. Trends over the years of diagnosis for [A] all primary treatment applied (%) and [B] use of both chemotherapy and radiotherapy (%), in patients with clinical stage II small cell lung cancer in the Netherlands, N = 472 (moving averages over 3 subsequent years)
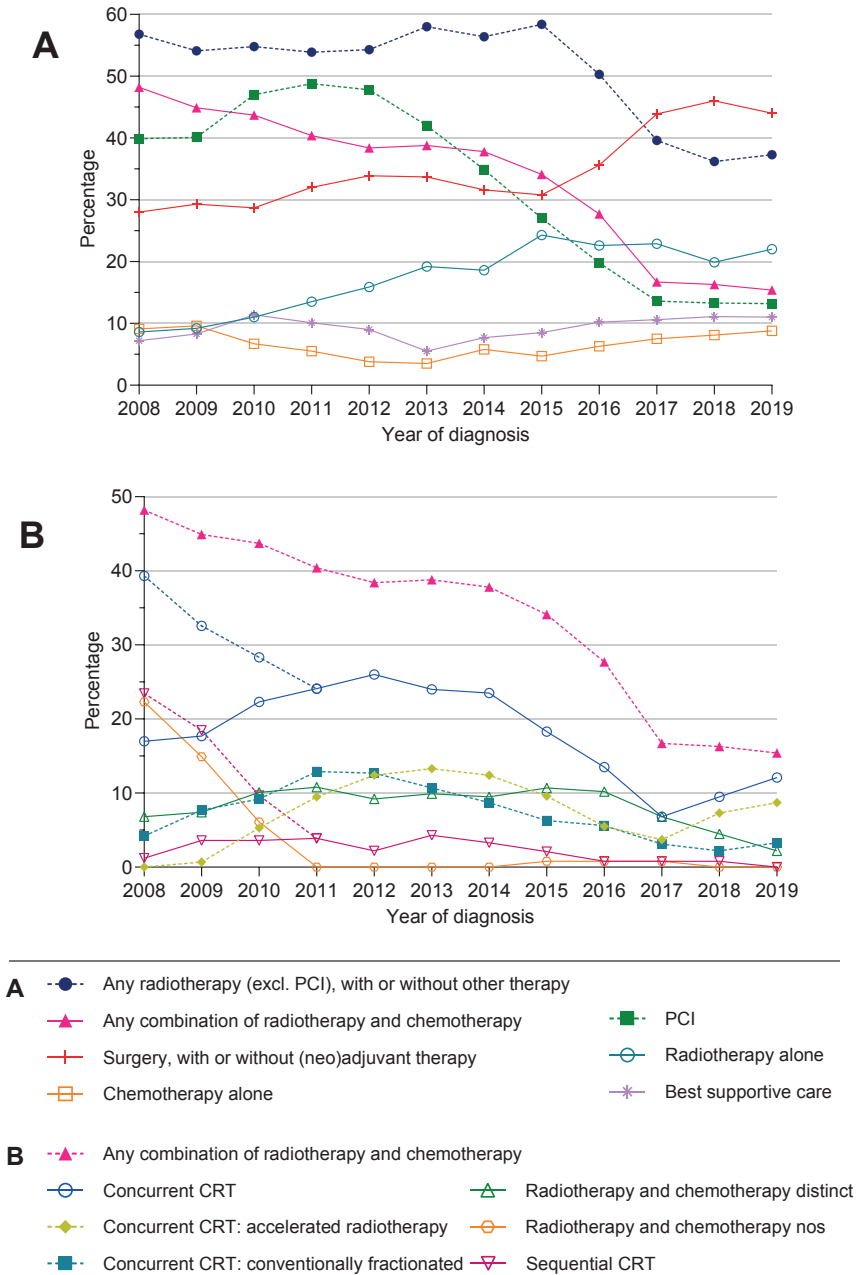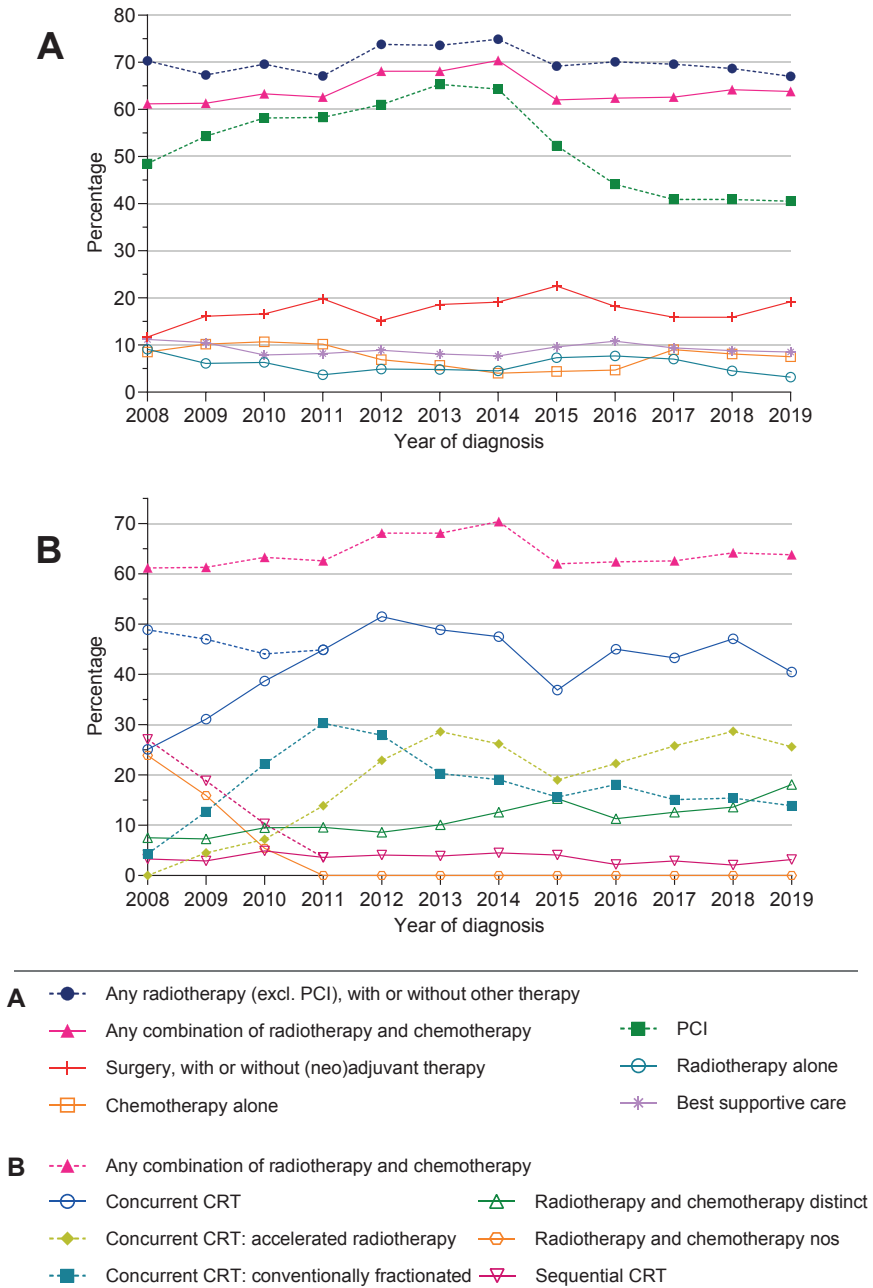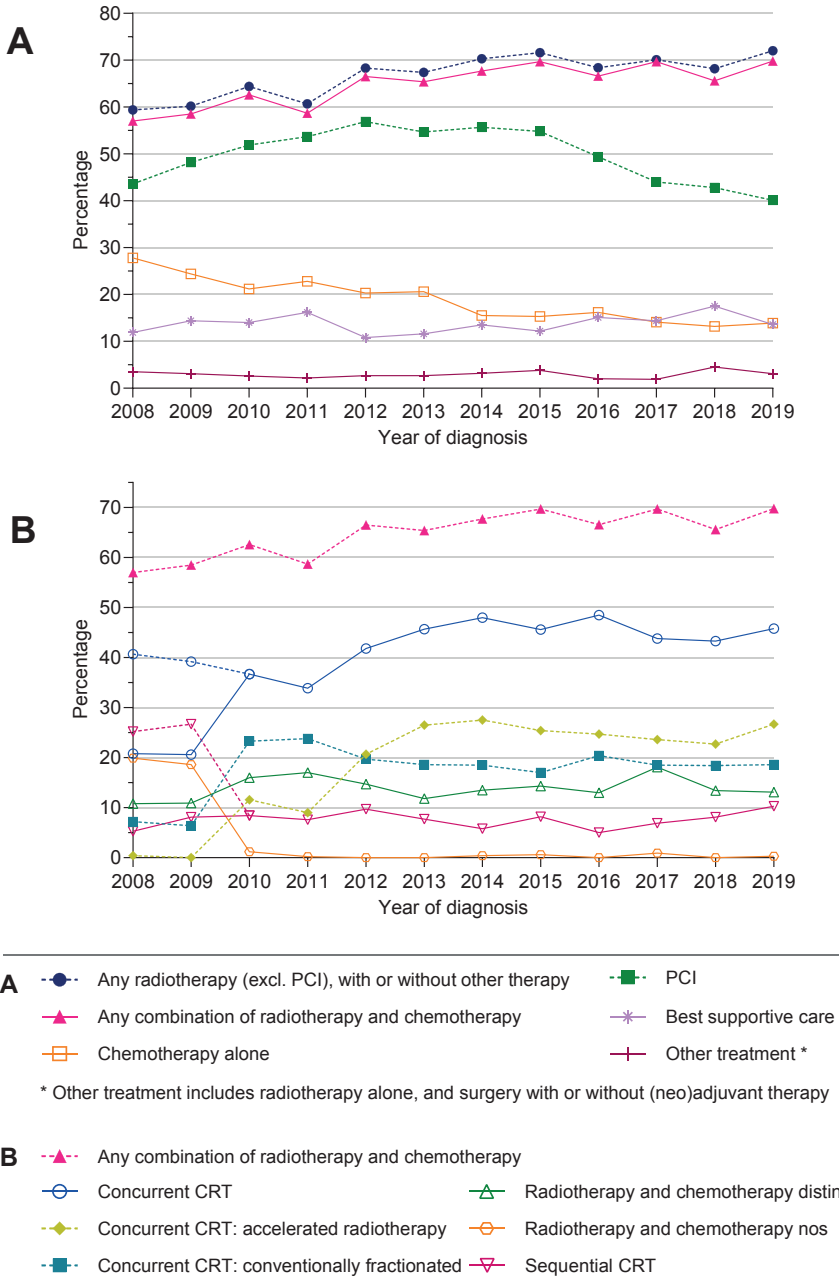
Clinical stage III

Figure 3. Trends over the years of diagnosis for [A] all primary treatment applied (%) and [B] use of both chemotherapy and radiotherapy (%), in patients with clinical stage III small cell lung cancer in the Netherlands, N = 5571

Concurrent and sequential chemoradiation

The variables strongest associated with cCRT versus sCRT in stage II-III were period of diagnosis ($OR_{2008-2011 \text{ vs } 2016-2019}$: 0.53), age at diagnosis ($OR_{\geq 80 \text{ vs } <60 \text{years}}$: 0.13) and WHO performance status ($OR_{\geq 2 \text{ vs } 0}$: 0.23) (Table 2). The likelihood of receiving cCRT instead of sCRT ranged by region: ORs were 0.52-1.72. Patients diagnosed in a university hospital or hospital with in-house radiotherapy had a higher probability of receiving cCRT. Also ≥30 minutes of travel time for radiotherapy compared to <15 minutes was associated with less cCRT.

Table 2. Odds ratios (OR) of receiving concurrent chemoradiation (CRT) compared to sequential CRT in patients diagnosed with small cell lung cancer clinical stage II-III in the Netherlands between 2008 and 2019

	Concurrent CRT		Sequential CRT		Crude		Adjusted [A]	
	N = 2,365		N = 437					
	n	*(%)*	*n*	*(%)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
Sex								
Male	1,084	(45.8)	203	(46.5)	Reference		Reference	
Female	1,281	(54.2)	234	(53.5)	1.03	(0.84-1.26)	0.90	(0.73-1.11)
Age at diagnosis, years [B]								
<60	713	(30.1)	93	(21.3)	Reference		Reference	
60 – 69	1,030	(43.6)	159	(36.4)	0.84	(0.64-1.11)	0.80	(0.60-1.05)
70 – 74	377	(15.9)	78	(17.8)	**0.63**	**(0.46-0.87)**	**0.58**	**(0.42-0.81)**
75 – 79	206	(8.7)	76	(17.4)	**0.35**	**(0.25-0.50)**	**0.30**	**(0.21-0.43)**
≥80	39	(1.6)	31	(7.1)	**0.16**	**(0.10-0.28)**	**0.13**	**(0.08-0.23)**
Period of diagnosis								
2008 – 2011	604	(25.5)	152	(34.8)	**0.62**	**(0.48-0.80)**	**0.53**	**(0.41-0.69)**
2012 – 2015	920	(38.9)	154	(35.2)	0.93	(0.72-1.20)	0.85	(0.66-1.10)
2016 – 2019	841	(35.6)	131	(30.0)	Reference		Reference	
Region								
North	344	(14.5)	53	(12.1)	Reference		Reference	
East	428	(18.1)	96	(22.0)	**0.69**	**(0.48-0.99)**	0.73	(0.51-1.06)
South	635	(26.8)	63	(14.4)	**1.55**	**(1.05-2.29)**	**1.72**	**(1.16-2.57)**
South west	408	(17.3)	118	(27.0)	**0.53**	**(0.37-0.76)**	**0.52**	**(0.37-0.75)**
North west	550	(23.3)	107	(24.5)	0.79	(0.55-1.13)	0.84	(0.59-1.21)
One-way travel time for radiotherapy, minutes								
<15 minutes	905	(38.3)	160	(36.6)	Reference		Reference	
15 - <30 minutes	1,203	(50.9)	211	(48.3)	1.01	(0.81-1.26)	1.01	(0.81-1.26)
≥30 minutes	257	(10.9)	66	(15.1)	**0.69**	**(0.50-0.95)**	**0.69**	**(0.50-0.95)**
Median (p25, p75)	18.0	(11.0, 24.0)	18.0	(11.0, 25.0)	0.99	(0.98-1.00)	0.99	(0.98-1.00)

Continued

	Concurrent CRT		Sequential CRT		Crude		Adjusted [A]	
	N = 2,365		N = 437					
	n	(%)	n	(%)	OR	(95% CI)	OR	(95% CI)
Type of hospital of diagnosis								
University	236	(10.0)	29	(6.6)	Reference		Reference	
Non-university	2,129	(90.0)	408	(93.4)	**0.64**	**(0.43-0.96)**	**0.64**	**(0.43-0.96)**
In-house radiotherapy								
No	1,850	(78.2)	359	(82.2)	Reference		Reference	
Yes	515	(21.8)	78	(17.8)	1.28	(0.98-1.67)	**1.45**	**(1.06-1.98)**
Radiotherapy facility volume of SCLC treatments								
<16 patients annually	666	(28.2)	122	(28.0)	Reference		Reference	
≥16 patients annually	1,698	(71.8)	313	(72.0)	0.99	(0.79-1.25)	0.91	(0.69-1.18)
Number of comorbidities at diagnosis [C]								
0	60	(20.4)	8	(22.2)	Reference		D	D
1	110	(37.4)	9	(25.0)	1.63	(0.60-4.44)		
2	55	(18.7)	10	(27.8)	0.73	(0.27-1.99)		
≥3	69	(23.5)	9	(25.0)	1.02	(0.37-2.82)		
WHO performance status [E]								
0	350	(43.0)	33	(26.0)	Reference		Reference	
1	390	(47.9)	61	(48.0)	**0.60**	**(0.39-0.94)**	0.72	(0.45-1.14)
≥2	74	(9.1)	33	(26.0)	**0.21**	**(0.12-0.36)**	**0.23**	**(0.13-0.40)**

CRT: chemoradiation; CI: confidence interval; values in bold are statistically significant

A   The analyses on sex and period of diagnosis were corrected for age at diagnosis, the analysis on age at diagnosis was corrected for period of diagnosis and region, the analysis on region was corrected for radiotherapy facility volume of SCLC treatments, the analyses on travel time for radiotherapy and type of hospital of diagnosis were not corrected as none of the variables fullfeed the criteria for inclusion in the adjustment sets, the analysis on in-house radiotherapy was corrected for region and type of hospital of diagnosis, the analysis on radiotherapy facility volume of SCLC treatments was corrected for region and in-house radiotherapy, the analysis on WHO performance status was corrected for age at diagnosis and region

B   Crude and adjusted ORs are 0.49 (95% CI: 0.39-0.60) and 0.45 (95% CI: 0.36-0.56), respectively, for patients aged ≥70 years compared to those aged <70 years, and 0.36 (95% CI: 0.28-0.46) and 0.32 (95% CI: 0.24-0.41), respectively, for patients aged ≥75 years compared to those aged <75 years

C   Analyses in a subset of patients diagnosed until 2015 in the southern part of the Netherlands

D   No multivariable analyses were performed, considering the limited number of patients

E   Analyses in a subset of patients diagnosed since 2015

In 2008-2019, 45% of the patients with stage II-III disease treated with cCRT received accelerated radiotherapy and 44% conventionally fractionated radiotherapy. For the remaining 11% the fractionation scheme could not be determined.

The variables strongest associated with accelerated versus conventionally fractionated radiotherapy were period of diagnosis ($OR_{2008-2011 \text{ vs } 2016-2019}$: 0.21), region ($OR_{south \text{ vs } north}$: 4.13) and the volume of SCLC patients in the radiotherapy facility ($OR_{\geq16 \text{ vs } <16 \text{ SCLC patients/year}}$: 3.01) (Table 3). No differences between age groups were observed, except for those aged 75-79 years compared to <60 years (OR: 0.66). Both patients with ≥30 minutes of travel time for radiotherapy compared to <15 minutes and those with a WHO performance status of 1 compared to 0 were less likely to receive accelerated radiotherapy. Patients diagnosed in a hospital with in-house radiotherapy had a higher probability of receiving accelerated radiotherapy (OR: 1.42). Only 6% of these patients had chemotherapy administered somewhere else than their radiotherapy, compared to 93% of the patients diagnosed in a hospital without in-house radiotherapy.

Table 3. Odds ratios (OR) of receiving accelerated radiotherapy (RT) compared to conventionally fractionated RT as part of concurrent chemoradiation in patients diagnosed with small cell lung cancer clinical stage II-III in the Netherlands between 2008 and 2019

	Accelerated RT		Conventionally fractionated RT		Crude		Adjusted [A]	
	N = 1,069		N = 1,049					
	n	(%)	n	(%)	OR	(95% CI)	OR	(95% CI)
Sex								
Male	476	(44.5)	497	(47.4)	Reference		Reference	
Female	593	(55.5)	552	(52.6)	1.12	(0.95-1.33)	1.12	(0.95-1.33)
Age at diagnosis, years [B]								
<60	314	(29.4)	317	(30.2)	Reference		Reference	
60 – 69	482	(45.1)	450	(42.9)	1.08	(0.88-1.32)	1.01	(0.80-1.27)
70 – 74	168	(15.7)	167	(15.9)	1.02	(0.78-1.32)	0.90	(0.66-1.22)
75 – 79	89	(8.3)	100	(9.5)	0.90	(0.65-1.24)	**0.66**	**(0.45-0.96)**
≥80	16	(1.5)	15	(1.4)	1.08	(0.52-2.22)	0.63	(0.27-1.47)
Period of diagnosis								
2008 – 2011	107	(10.0)	324	(30.9)	**0.25**	**(0.19-0.32)**	**0.21**	**(0.16-0.28)**
2012 – 2015	504	(47.1)	379	(36.1)	1.00	(0.83-1.22)	0.96	(0.78-1.18)
2016 – 2019	458	(42.8)	346	(33.0)	Reference		Reference	
Region								
North	102	(9.5)	188	(17.9)	Reference		Reference	
East	195	(18.2)	185	(17.6)	**1.94**	**(1.42-2.66)**	**1.46**	**(1.05-2.03)**
South	447	(41.8)	138	(13.2)	**5.97**	**(4.39-8.12)**	**4.13**	**(3.00-5.70)**
South west	84	(7.9)	284	(27.1)	**0.55**	**(0.39-0.77)**	**0.59**	**(0.41-0.84)**
North west	241	(22.5)	254	(24.2)	**1.75**	**(1.30-2.36)**	1.37	(1.00-1.86)
One-way travel time for radiotherapy, minutes								
<15 minutes	428	(40.0)	400	(38.1)	Reference		Reference	
15 - <30 minutes	553	(51.7)	511	(48.7)	1.01	(0.84-1.21)	0.82	(0.67-1.00)
≥30 minutes	88	(8.2)	138	(13.2)	**0.60**	**(0.44-0.80)**	**0.63**	**(0.46-0.87)**
Median (p25, p75)	17.0	(11.0, 23.0)	18.0	(11.0, 25.0)	**0.98**	**(0.98-0.99)**	**0.98**	**(0.97-0.99)**
Type of hospital of diagnosis								
University	93	(8.7)	105	(10.0)	Reference		Reference	
Non-university	976	(91.3)	944	(90.0)	1.17	(0.87-1.56)	1.17	(0.87-1.56)

Continued

	Accelerated RT		Conventionally fractionated RT		Crude		Adjusted [A]	
	N = 1,069		N = 1,049					
	n	(%)	n	(%)	OR	(95% CI)	OR	(95% CI)
In-house radiotherapy								
No	900	(84.2)	780	(74.4)	Reference		Reference	
Yes	169	(15.8)	269	(25.6)	**0.54**	**(0.44-0.68)**	**1.42**	**(1.03-1.94)**
Radiotherapy facility volume of SCLC treatments								
<16 patients annually	142	(13.3)	439	(41.9)	Reference		Reference	
≥16 patients annually	927	(86.7)	609	(58.1)	**4.71**	**(3.80-5.84)**	**3.01**	**(2.38-3.79)**
Number of comorbidities at diagnosis [D]								
0	34	(17.9)	16	(22.9)	Reference		C	C
1	77	(40.5)	24	(34.3)	1.51	(0.71-3.20)		
2	38	(20.0)	10	(14.3)	1.79	(0.72-4.47)		
≥3	41	(21.6)	20	(28.6)	0.96	(0.43-2.15)		
WHO performance status [E]								
0	216	(47.6)	121	(37.0)	Reference		Reference	
1	201	(44.3)	177	(54.1)	**0.64**	**(0.47-0.86)**	**0.50**	**(0.35-0.71)**
≥2	37	(8.1)	29	(8.9)	0.71	(0.42-1.22)	0.54	(0.28-1.04)

RT: radiotherapy; CI: confidence interval; values in bold are statistically significant

A   The analyses on sex and type of hospital of diagnosis were not corrected as none of the variables fullfeed the criteria for inclusion in the adjustment sets, the analysis on age at diagnosis was corrected for period of diagnosis, region and radiotherapy facility volume of SCLC treatments, the analyses on period of diagnosis and radiotherapy facility volume of SCLC treatments were corrected for region, the analysis on region was corrected for radiotherapy facility volume of SCLC treatments, the analysis on travel time for radiotherapy was corrected for in-house radiotherapy and radiotherapy facility volume of SCLC treatments, the analysis on in-house radiotherapy was corrected for region, type of hospital of diagnosis and radiotherapy facility volume of SCLC treatments, the analysis for WHO performance status was corrected for region and radiotherapy facility volume of SCLC treatments

B   Crude and adjusted ORs are 0.93 (95% CI: 0.77-1.13) and 0.79 (95% CI: 0.63-1.0.99), respectively, for patients aged ≥70 years compared to those aged <70 years, and 0.88 (95% CI: 0.67-1.17) and 0.65 (95% CI: 0.48-0.92), respectively, for patients aged ≥75 years compared to those aged <75 years

C   No multivariable analyses were performed, considering the limited number of patients

D   Analyses in a subset of patients diagnosed until 2015 in the southern part of the Netherlands

E   Analyses in a subset of patients diagnosed since 2015

In 2008-2009, not all combinations of chemotherapy and radiotherapy could be classified as CRT (cCRT/sCRT) or distinct therapies. Nevertheless, sensitivity analyses showed comparable estimates for the multivariable analyses when including only 2010-2019 (Supplementary Table 1 and 2).

DISCUSSION

This study describes recent trends and variations in treatment strategies for stage I-III SCLC in the Netherlands. An increased use of surgery and decreased combined use of chemotherapy and radiotherapy was observed in stage I disease, while the combined use of chemotherapy and radiotherapy remained stable in stage II and increased in stage III disease. Most patients with stage II-III disease received cCRT in a hyperfractionated accelerated scheme since 2012.

Similarly to our results, the use of surgery in stage I increased in the USA [19,20] from 14.9% (2004) to 28.5% (2013) [19]. This trend is in line with current treatment guidelines considering surgery with adjuvant chemotherapy as a treatment option in T1-2N0-tumors [6-8], as relatively favorable survival outcomes were reported in cohorts and historical series [21-25]. In our study, an increasing percentage of patients with stage I disease had a pathology confirmation before surgery. This suggests that a decreasing number of patients had their surgery based on an initial non-small cell lung cancer (NSCLC) diagnosis, but no data was available on whether the initial diagnosis upon (central) revision of pathology was NSCLC instead of SCLC. SBRT followed by chemotherapy may nowadays also be used [6], despite limited evidence [26]. In our study, one third of all irradiated patients with stage I disease received SBRT, mostly without adjuvant chemotherapy. The use of radiotherapy alone in stage I, increased over time. Reasons for not administering chemotherapy were not available. In the USA, half of the stage I patients receiving SBRT also had chemotherapy administered, 43% of whom prior to SBRT [19].

Our study demonstrates that combined use of chemotherapy and radiotherapy increased in stage III disease, which concerns the majority of patients included. Increased use of both modalities was already observed in the period 1997-2007 in the Netherlands, as well as in 2004-2011 in England [27,28]. Unfortunately, details on CRT variations lacked in these studies [27,28], and CRT could not be distinguished from chemotherapy followed by PCI [28]. We found that 39-42% of the patients with stage II-III disease received cCRT and 3-8% sCRT. Furthermore, the use of cCRT versus sCRT increased over time and varied between patient groups, hospitals, and geographic regions. Variation in SCLC treatment within a country was also demonstrated in England, where chemotherapy regimens and administration varied between hospital networks [29].

Until 2012, a minority of patients with stage II-III disease received cCRT in a hyperfractionated accelerated scheme. This corresponds with the limited use of twice-daily cCRT reported for the USA until 2012, where only 11% of the patients with non-metastatic disease received twice-daily radiotherapy [30]. Limited use may reflect logistic challenges of a twice-daily regimen, concerns about its toxicity [10,11], or doubt about the reported benefit of the accelerated fractionation arm in the Turrisi-trial [9], as a relatively low dose was administered in the once-daily arm (45Gy in 25 fractions). The more recent CONVERT-trial revealed no statistically significant difference in survival between twice-daily and once-daily radiotherapy with a higher total dose (66Gy in 33 fractions) [31]. The toxicity rates were comparable between both arms and lower than in the Turrisi-trial. As the CONVERT-trial was powered to demonstrate superiority of once-daily radiotherapy and not equivalence, it should not be an argument to justify administering once-instead of twice-daily cCRT. The first trial results were presented in 2015 and most patients treated with cCRT in the Netherlands received accelerated radiotherapy since 2012. Reassuringly, we found no difference in the use of accelerated versus conventionally fractionated cCRT between 2012-2015 and 2016-2019 in multivariable analyses, suggesting that the trial results were not commonly used for falsely justifying once-daily cCRT in Dutch clinical practice.

Among patient-related factors, WHO performance status was most strongly associated with variation in fractionation schemes. In a recent European expert panel, fitness of patients was also identified as an important decision criterion for the choice of radiotherapy fractionation [32]. Variation was furthermore present between regions and radiotherapy facilities, which corresponds with the finding of the expert panel on a lack of uniform treatment decision regarding fractionation schemes in radiotherapy facilities across Europe [32].

Although the benefit of PCI in limited stage SCLC was already demonstrated in 1999 [12], our study shows an increase in use of PCI during 2008-2012, which might reflect increased attention to PCI after publication of a randomized trial in 2007 showing its benefit in extensive disease [33]. Nevertheless, between 2012 and 2019, the use of PCI substantially decreased in stage I-III disease following concerns about neurocognitive decline [13] and its reported lack of survival benefit in stage IV disease when compared to only MRI follow-up of the brain [14]. This decreasing trend in the Netherlands has previously been described comprehensively [15].

Between 2008 and 2019, the proportion of diagnoses with stage III disease decreased while the proportion of stage IV disease increased. This shift probably

reflects changes in staging by different TNM editions applicable in the study period: tumors with pleural effusion were classified T4 (in combination with N0: stage IIIB) in TNM6 (2008-2009) and M1 (stage IV) in TNM7-8. In patients with malignant pleural effusion, chemotherapy need to be considered instead of CRT [34], causing a relatively lower use of CRT in stage III in 2008-2009. Also, diagnostic procedures in clinical practice improved over time, like screening for brain metastases with a brain-MRI instead of CT-scan. This resulted in more accurate staging of the disease and as such stage migration [35], favoring the treatability of patients in the study population diagnosed in more recent years. A future study may look into treatment outcomes.

The variations in treatment patterns observed in the current study were addressed in the Dutch Association of Radiation Oncology's division of lung cancer, and radiotherapy facilities were provided the opportunity to receive feedback on treatments applied in their region compared to other regions. Variation in clinical practice may reflect the preferences of patients or physicians. Both twice-daily radiotherapy and cCRT may be logistically challenging, the latter in case chemotherapy and radiotherapy are provided by different institutes, which requires patients to visit both a hospital and a radiotherapy facility on certain treatment days. To investigate the consequences of treatment variation, a future study may relate the variation in clinical practice to treatment outcomes. This may also provide insight in unwarranted aspects of variation.

Our study may have misclassified conventionally fractionated radiotherapy as accelerated, in case treatment was terminated prematurely after 15-28 days. This differential misclassification probably affected frail and elderly patients who are at the highest risk of treatment associated toxicity [36] and therefore most likely to terminate treatment prematurely. Falsely classifying these patients as having received accelerated radiotherapy may consequently have biased the analyses on WHO performance status and age presented in Table 3.

Another limitation regards the limited availability of comorbidities and WHO performance status which hampered both adjusting analyses for these factors and performing multivariable analyses on comorbidities, resulting in residual confounding. As the comorbidities and WHO performance status were available only for subsets of patients diagnosed in a specific region and/or years, the analyses on these variables may not necessarily be generalizable to the total study population. Nevertheless, it is not expected that these subsets

differ from other patients in the Netherlands diagnosed in the study period. Comorbidities may furthermore be underreported in the hospitals' medical records, causing non-differential misclassification. However, we assume that the comorbidities relevant for treatment decision are registered, hence the effect of this misclassification is expected to be limited.

A final limitation of our study concerns having information available only on the delivered but not on the intended treatment. As a consequence, we cannot report on treatment adjustments nor provide direct insights in the process of treatment decision. We present factors associated with the treatments given and it should be noted that another treatment may initially be decided on.

Conclusions

This nationwide population-based study demonstrates increased use of surgery in stage I SCLC in 2008-2019. Combined use of chemotherapy and radiotherapy decreased in stage I, remained constant in stage II and increased in stage III disease. In 2019, 46% of the patients with stage III disease received cCRT, the majority of whom with accelerated radiotherapy. We identified patient groups who were more likely to receive cCRT versus sCRT and showed variation between hospitals and geographical regions. Choice of fractionation schemes was associated with patients' fitness, radiotherapy facilities' volume for SCLC, and geographical regions. Treatment variations were fed back to the radiation oncologists of the nationwide division of lung cancer. A future study may relate the variation observed to treatment outcomes, to investigate the consequences of treatment variation. Possible unwarranted treatment variation should subsequently be countered.

ACKNOWLEDGEMENTS

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Concurrent chemoradiation definitions:
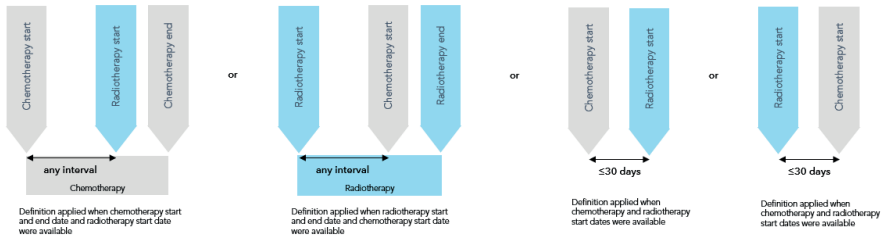
Sequential chemoradiation definitions:
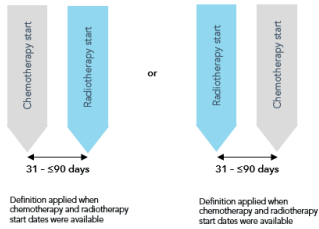
Distinct chemotherapy and radiotherapy definitions:
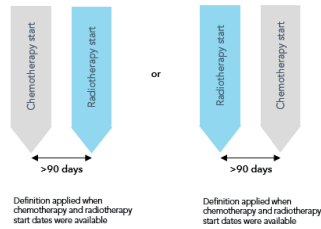
- PCI and SBRT were not considered part of chemoradiation
- In case of a missing starting date, treatments were classified as chemotherapy and radiotherapy not otherwise specified (nos).
- In case chemotherapy and radiotherapy met the definition of both concurrent and sequential/distinct treatment, it was classified as concurrent

Supplementary Figure 1. Definitions applied to classify the different treatment scenarios using combinations of chemotherapy and radiotherapy
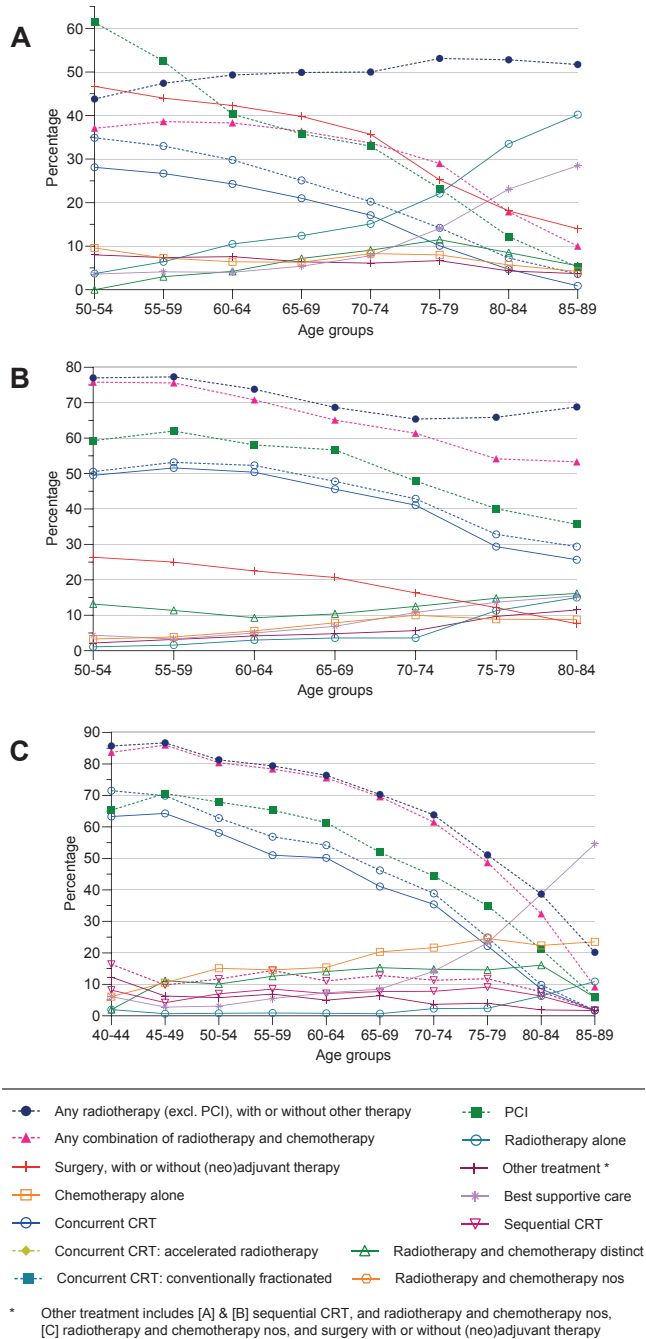
Supplementary Figure 2. Trends for primary treatment of small cell lung cancer according to age groups, stratified for patients with [A] clinical stage I (N = 524), [B] clinical stage II (N = 451) and [C] clinical stage III (N = 5547) in the Netherlands; [A] and [B] present moving averages over 3 subsequent age categories; age groups with less than 15 patients were not shown

Supplementary Table 1. Odds ratios (OR) of receiving concurrent chemoradiation (CRT) compared to sequential CRT in patients diagnosed with small cell lung cancer clinical stage II-III in the Netherlands between 2010 and 2019

	Concurrent CRT		Sequential CRT		Crude		Adjusted [A]	
	N = 2,129		N = 363					
	n	(%)	n	(%)	OR	(95% CI)	OR	(95% CI)
Sex								
Male	975	(45.8)	165	(45.5)	Reference		Reference	
Female	1,154	(54.2)	198	(54.5)	0.99	(0.79-1.23)	0.85	(0.67-1.07)
Age at diagnosis, years [B]								
<60	624	(29.3)	70	(19.3)	Reference		Reference	
60 – 69	937	(44.0)	126	(34.7)	0.83	(0.61-1.14)	0.81	(0.59-1.10)
70 – 74	340	(16.0)	69	(19.0)	**0.55**	**(0.39-0.79)**	**0.53**	**(0.37-0.76)**
75 – 79	191	(9.0)	69	(19.0)	**0.31**	**(0.21-0.45)**	**0.28**	**(0.19-0.40)**
≥80	37	(1.7)	29	(8.0)	**0.14**	**(0.08-0.25)**	**0.12**	**(0.07-0.21)**
Period of diagnosis								
2010 – 2011	368	(17.3)	78	(21.5)	0.73	(0.54-1.00)	**0.64**	**(0.46-0.87)**
2012 – 2015	920	(43.2)	154	(42.4)	0.93	(0.72-1.20)	0.85	(0.65-1.09)
2016 – 2019	841	(39.5)	131	(36.1)	Reference		Reference	
Region								
North	291	(13.7)	39	(10.7)	Reference		Reference	
East	384	(18.0)	73	(20.1)	0.70	(0.46-1.07)	0.76	(0.50-1.16)
South	610	(28.7)	58	(16.0)	1.41	(0.92-2.17)	**1.59**	**(1.02-2.47)**
South west	364	(17.1)	102	(28.1)	**0.48**	**(0.32-0.71)**	**0.47**	**(0.31-0.70)**
North west	480	(22.5)	91	(25.1)	0.71	(0.47-1.06)	0.76	(0.51-1.15)
One-way travel time for radiotherapy, minutes								
<15 minutes	823	(38.7)	138	(38.0)	Reference		Reference	
15 - <30 minutes	1,082	(50.8)	176	(48.5)	1.03	(0.81-1.31)	1.03	(0.81-1.31)
≥30 minutes	224	(10.5)	49	(13.5)	0.77	(0.54-1.10)	0.77	(0.54-1.10)
Median (p25, p75)	17.0	(11.0, 24.0)	18.0	(11.0, 25.0)	1.00	(0.98-1.01)	1.00	(0.98-1.01)
Type of hospital of diagnosis								
University	193	(9.1)	25	(6.9)	Reference		Reference	
Non-university	1,936	(90.9)	338	(93.1)	0.74	(0.48-1.14)	0.74	(0.48-1.14)
In-house radiotherapy								
No	1,703	(80.0)	299	(82.4)	Reference		Reference	
Yes	426	(20.0)	64	(17.6)	1.17	(0.87-1.56)	1.36	(0.97-1.93)
Radiotherapy facility volume of SCLC treatments								
<16 patients annually	581	(27.3)	98	(27.1)	Reference		Reference	
≥16 patients annually	1,547	(72.7)	264	(72.9)	0.99	(0.77-1.27)	0.85	(0.63-1.14)
Number of comorbidities at diagnosis [C]								
0	52	(18.8)	7	(20.6)	Reference		D	D
1	106	(38.4)	9	(26.5)	1.59	(0.56-4.49)		
2	52	(18.8)	10	(29.4)	0.70	(0.25-1.98)		
≥3	66	(23.9)	8	(23.5)	1.11	(0.38-3.26)		

Continued

	Concurrent CRT		Sequential CRT		Crude		Adjusted [A]	
	N = 2,129		N = 363					
	n	(%)	n	(%)	OR	(95% CI)	OR	(95% CI)
WHO performance status [E]								
0	350	(43.0)	33	(26.0)	Reference		Reference	
1	390	(47.9)	61	(48.0)	0.60	(0.39-0.94)	0.72	(0.45-1.14)
≥2	74	(9.1)	33	(26.0)	**0.21**	**(0.12-0.36)**	**0.23**	**(0.13-0.40)**

CRT: chemoradiation; CI: confidence interval; values in bold are statistically significant

A   The analyses on sex and period of diagnosis were corrected for age at diagnosis, the analysis on age at diagnosis was corrected for period of diagnosis and region, the analysis on region was corrected for radiotherapy facility volume of SCLC treatments, the analyses on travel time for radiotherapy and type of hospital of diagnosis were not corrected as none of the variables fullfeed the criteria for inclusion in the adjustment sets, the analysis on in-house radiotherapy was corrected for region and type of hospital of diagnosis, the analysis on radiotherapy facility volume of SCLC treatments was corrected for region and in-house radiotherapy, the analysis on WHO performance status was corrected for age at diagnosis and region

B   Crude and adjusted ORs are 0.43 (95% CI: 0.34-0.54) and 0.41 (95% CI: 0.32-0.51), respectively, for patients aged ≥70 years compared to those aged <70 years, and 0.32 (95% CI: 0.25-0.42) and 0.30 (95% CI: 0.22-0.39), respectively, for patients aged ≥75 years compared to those aged <75 years

C   Analyses in a subset of patients diagnosed until 2015 in the southern part of the Netherlands

D   No multivariable analyses were performed, considering the limited number of patients

E   Analyses in a subset of patients diagnosed since 2015

Supplementary Table 2. Odds ratios (OR) of receiving accelerated radiotherapy (RT) compared to conventionally fractionated RT as part of concurrent chemoradiation in patients diagnosed with small cell lung cancer clinical stage II-III in the Netherlands between 2010 and 2019

	Accelerated RT		Conventionally fractionated RT		Crude		Adjusted [A]	
	N = 1,067		N = 974					
	n	*(%)*	*n*	*(%)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
Sex								
Male	474	(44.4)	461	(47.3)	Reference		Reference	
Female	593	(55.6)	513	(52.7)	1.12	(0.94-1.34)	1.12	(0.94-1.34)
Age at diagnosis, years [B]								
<60	314	(29.4)	284	(29.2)	Reference		Reference	
60 – 69	481	(45.1)	420	(43.1)	1.04	(0.84-1.27)	0.98	(0.77-1.24)
70 – 74	167	(15.7)	159	(16.3)	0.95	(0.73-1.24)	0.88	(0.65-1.19)
75 – 79	89	(8.3)	97	(10.0)	0.83	(0.60-1.15)	**0.64**	**(0.44-0.93)**
≥80	16	(1.5)	14	(1.4)	1.03	(0.50-2.16)	0.64	(0.28-1.50)
Period of diagnosis								
2008 – 2011	105	(9.8)	249	(25.6)	**0.32**	**(0.24-0.42)**	**0.26**	**(0.19-0.35)**
2012 – 2015	504	(47.2)	379	(38.9)	1.00	(0.83-1.22)	0.96	(0.78-1.18)
2016 – 2019	458	(42.9)	346	(35.5)	Reference		Reference	
Region								
North	102	(9.6)	177	(18.2)	Reference		Reference	
East	194	(18.2)	177	(18.2)	**1.90**	**(1.38-2.61)**	**1.43**	**(1.03-1.99)**
South	446	(41.8)	137	(14.1)	**5.65**	**(4.14-7.70)**	**3.88**	**(2.80-5.37)**
South west	84	(7.9)	264	(27.1)	**0.55**	**(0.39-0.78)**	**0.60**	**(0.42-0.85)**
North west	241	(22.6)	219	(22.5)	**1.91**	**(1.41-2.59)**	**1.47**	**(1.07-2.02)**
One-way travel time for radiotherapy, minutes								
<15 minutes	428	(40.1)	372	(38.2)	Reference		Reference	
15 - <30 minutes	551	(51.6)	475	(48.8)	1.01	(0.84-1.21)	0.82	(0.67-1.00)
≥30 minutes	88	(8.2)	127	(13.0)	**0.60**	**(0.44-0.82)**	**0.66**	**(0.47-0.91)**
Median (p25, p75)	17.0	(11.0, 23.0)	17.5	(11.0, 25.0)	**0.98**	**(0.98-0.99)**	**0.98**	**(0.97-0.99)**
Type of hospital of diagnosis								
University	92	(8.6)	92	(9.4)	Reference		Reference	
Non-university	975	(91.4)	882	(90.6)	1.11	(0.82-1.50)	1.11	(0.82-1.50)
In-house radiotherapy								
No	899	(84.3)	729	(74.8)	Reference		Reference	
Yes	168	(15.7)	245	(25.2)	**0.56**	**(0.45-0.69)**	**1.44**	**(1.05-1.99)**
Radiotherapy facility volume of SCLC treatments								
<16 patients annually	142	(13.3)	410	(42.1)	Reference		Reference	
≥16 patients annually	925	(86.7)	563	(57.9)	**4.74**	**(3.82-5.90)**	**3.04**	**(2.41-3.85)**
Number of comorbidities at diagnosis [C]								
0	34	(17.9)	15	(22.1)	Reference		D	D
1	77	(40.5)	23	(33.8)	1.48	(0.69-3.18)		
2	38	(20.0)	10	(14.7)	1.68	(0.67-4.22)		
≥3	41	(21.6)	20	(29.4)	0.90	(0.40-2.03)		

Continued

	Accelerated RT		Conventionally fractionated RT		Crude		Adjusted [A]	
	N = 1,067		N = 974					
	n	(%)	n	(%)	OR	(95% CI)	OR	(95% CI)
WHO performance status [E]								
0	216	(47.6)	121	(37.0)	Reference		Reference	
1	201	(44.3)	177	(54.1)	**0.64**	**(0.47-0.86)**	**0.50**	**(0.35-0.71)**
≥2	37	(8.1)	29	(8.9)	0.71	(0.42-1.22)	0.54	(0.28-1.04)

RT: radiotherapy; CI: confidence interval; values in bold are statistically significant

A   The analyses on sex and type of hospital of diagnosis were not corrected as none of the variables fullfeed the criteria for inclusion in the adjustment sets, the analysis on age at diagnosis was corrected for period of diagnosis, region and radiotherapy facility volume of SCLC treatments, the analyses on period of diagnosis and radiotherapy facility volume of SCLC treatments were corrected for region, the analysis on region was corrected for radiotherapy facility volume of SCLC treatments, the analysis on travel time for radiotherapy was corrected for in-house radiotherapy and radiotherapy facility volume of SCLC treatments, the analysis on in-house radiotherapy was corrected for region, type of hospital of diagnosis and radiotherapy facility volume of SCLC treatments, the analysis for WHO performance status was corrected for region and radiotherapy facility volume of SCLC treatments

B   Crude and adjusted ORs are 0.89 (95% CI: 0.73-1.09) and 0.79 (95% CI: 0.63-0.98), respectively, for patients aged ≥70 years compared to those aged <70 years, and 0.85 (95% CI: 0.64-1.13) and 0.66 (95% CI: 0.48-0.91), respectively, for patients aged ≥75 years compared to those aged <75 years

C   Analyses in a subset of patients diagnosed until 2015 in the southern part of the Netherlands

D   No multivariable analyses were performed, considering the limited number of patients

E   Analyses in a subset of patients diagnosed since 2015

CHAPTER

4

Breast conserving surgery with
radiotherapy in DCIS grade I-II

DE-INTENSIFICATION OF RADIOTHERAPY USE IN TREATMENT OF DCIS IN THE NETHERLANDS – A NATIONWIDE OVERVIEW FROM 2008 UNTIL 2022

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ABSTRACT

Background

Ductal Carcinoma In-Situ (DCIS) is treated by breast-conserving surgery (BCS) followed by radiotherapy or mastectomy to prevent progression to invasive breast cancer. However, most DCIS never will progress and post-BCS radiotherapy does not improve survival. Treatment de-intensification is therefore obvious. We evaluated radiotherapy use in the Netherlands at the current times of treatment de-intensification.

Methods

Women diagnosed with DCIS in 2008-2022 were identified in the Netherlands Cancer Registry. Their primary treatments were presented over time and for age groups, stratified for DCIS grade I-II and III. Factors associated with post-BCS radiotherapy use and boost irradiation use in post-BCS whole breast irradiation were identified.

Results

In DCIS grade I-II (N=16,653), surgery was more often omitted in recent years (30% in 2022). The use of BCS without radiotherapy increased from ~11% in 2008-2013 to ~26% in 2017-2022. Furthermore, post-BCS radiotherapy increasingly concerned whole breast irradiation without boost and partial breast irradiation. In women with DCIS grade III (N=13,534), BCS without radiotherapy only slightly increased in the most recent years in older patients, while boost irradiation was increasingly omitted. Post-BCS radiotherapy and boost irradiation were more often applied in case of a higher risk of (invasive) recurrences: young age, larger lesions, irradical resection. Variation was observed for hospital-characteristics but not for regions.

Conclusion

In DCIS, de-intensification of radiotherapy after BCS is clearly ongoing, by applying radiotherapy less often or by using partial breast irradiation or omitting a boost. These effects are more prominent in older women and those with grade I-II DCIS.

INTRODUCTION

Ductal Carcinoma In-Situ (DCIS) is frequently diagnosed in countries with a screening program for breast cancer. DCIS accounts for ~20-25% of all breast neoplasms in the US [1] and ~12% in the Netherlands [2]. Each year, around 2,300 women in the Netherlands are diagnosed with DCIS [2,3], of which about 80% is detected by the population-based breast cancer screening in women aged between 50 and 75 [3,4].

DCIS is treated by breast-conserving surgery (BCS), often with post-operative radiotherapy, or mastectomy to prevent invasive and non-invasive recurrences [5-7]. However, the majority of DCIS will never cause symptoms or progress to invasive breast cancer [8-10]. Also, post-BCS radiotherapy does not affect breast cancer-specific and overall survival, even though reducing the local recurrence risk [11-15]. Hence, the optimal management of DCIS is debated and efforts were taken in de-intensifying treatment to prevent the burden of (over)treatment in low-risk disease [16-19]. First, the LORD (NCT02492607), COMET (NCT02926911), LORETTA (JCOG1505), and LORIS (UKCRN16736) trials are investigating whether active surveillance in low-risk DCIS (grade I-II) is safe [20-23]. Second, there has been an increasing tendency to forgo radiotherapy in women at low risk of (invasive) recurrence who underwent BCS [7,24,25]. Third, in women treated with BCS followed by radiotherapy, de-intensification can be considered by providing partial breast irradiation (PBI) instead of whole breast irradiation (WBI) in selected low-risk patients [7,26], or by omission of an extra dose of radiotherapy (boost) in WBI [27,28].

These de-intensification efforts changed the use of radiotherapy in DCIS treatment in the Netherlands, as illustrated in a comprehensive overview of DCIS diagnosed at screenings ages between 1989 and 2018 [13]. Decreased post-BCS radiotherapy use was observed in DCIS grade I-II, whereas in grade III DCIS the use remained stable. However, variation in administration of post-BCS radiotherapy, trends in use of PBI and WBI with/without boost irradiation, and use of radiotherapy in subsequent years were not investigated. The use of a boost after BCS was evaluated between 2011 and 2016: higher risk patients (aged <50, with larger or higher graded DCIS or irradical resection) had a higher probability of receiving a boost than patients at low-risk, and over time similar use was found [29]. To provide further insight in radiotherapy utilization in DCIS treatment in the current era of treatment de-

intensification, our study investigates overall radiotherapy use as well as use of PBI or WBI with and without a boost. Overviews in the context of primary treatment trends over time and according to age groups are provided, as well as insights in variation of radiotherapy use following BCS and use of a boost in WBI.

MATERIALS AND METHODS

Patients

Women diagnosed with DCIS between January 1, 2008 and December 31, 2022 were identified in the Netherlands Cancer Registry. This population-based registry contains information on patient, hospital, disease and primary treatment of all patients diagnosed with cancer in the Netherlands. Data are gathered directly from the medical records by trained registrars in all Dutch hospitals. Women with unknown DCIS grade, living abroad, diagnosed or treated abroad, or diagnosed during autopsy were excluded from the current study.

Definitions

Characteristics of patients, hospitals of diagnosis, and disease were described stratified for DCIS grade I-II and III, based on the resection specimen or otherwise biopsy and using the Bloom-Richardson grading system [30]. We presented DCIS grade I and II combined, considering the difficulty for pathologists to distinguish between grade I and II [38] and the fact that both are often considered low-grade disease. Patients' residences (based on postal code) at time of diagnoses were classified into five regions (Supplementary Figure 1), each including ≥ 3 radiotherapy facilities and ≥ 11 hospitals, of which ≥ 1 university hospital. Comorbidities were available only in the South-region before 2017, and categorized based on the Charlson Comorbidity Index [31] (Supplementary Table 1). One-way travel time for radiotherapy was calculated using the GEODAN 2013-drive time matrix [32] and postal codes of patients' residence and the nearest radiotherapy facility. Hospitals of diagnoses and surgery were classified by 1) type: university, including the single cancer-specific hospital in the Netherlands, or non-university, 2) presence or absence of a radiotherapy department, not including radiotherapy facilities of other institutes in the same building as radiotherapy presence, and 3) average annual hospital volume of DCIS diagnoses in the study period, categorized as either low, intermediate or high volume using tertiles. DCIS size regarded pathological size. Resection

margin status was defined as either: R0, R1 with focal residual disease (into the inked margin in an area of ≤4 mm), or R1 with more than focal residual disease.

Primary treatment was categorized as BCS with radiotherapy, BCS without radiotherapy, mastectomy with radiotherapy, mastectomy without radiotherapy, BCS followed by mastectomy (with/without radiotherapy), and no surgery (with/without radiotherapy). For patients diagnosed since 2011, radiotherapy following BCS could further be divided by WBI with or without use of a boost, and PBI.

Analyses

Primary treatment was presented over time and by age groups, stratified for DCIS grade I-II and III. In order to assess variation in 1) radiotherapy use following BCS and 2) boost irradiation in post-BCS WBI, multilevel logistic regression analyses were performed, stratified for DCIS grade I-II and III. These analyses correct for the nesting of patients within hospitals. Women who underwent mastectomy following BCS were excluded from the multilevel logistic regression analyses. Distinct models were created for each association investigated, including both a random effect and random intercept for the various hospitals if the corrected Akaike Information Criterion (AICc)-statistic improved compared to the model with a random intercept only. Sets of variables for adjustment were selected for each model separately. A variable was included in the multivariable analyses when univariable inclusion changed the odds ratio (OR) of interest with at least 5% compared to the unadjusted multilevel OR. Final ORs were presented with accompanying 95% confidence intervals (95%CIs), reflecting a p-value <0.05 to be statistically significant. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

RESULTS

In the period 2008-2022, 16,653 women were diagnosed with DCIS grade I-II and 13,534 with grade III. The proportion of grade I-II diagnoses increased over time (Supplementary Figure 2). Most women were diagnosed at ages eligible for the nationwide breast cancer screening program (50-75 years): 79% in grade I-II, 82% in grade III (Table 1). DCIS grade I-II was more often sized ≤2.5 cm (75%) than DCIS grade III (60%), while palpability did not differ. In DCIS grade I-II compared to III, surgery was less often applied: 88% versus 98%. The proportion R0-resection was similar between the groups.

Table 1. Patient, hospital, and disease characteristics, for women diagnosed with ductal carcinoma in-situ (DCIS) in the Netherlands (N=30,187), stratified for grade I-II and III

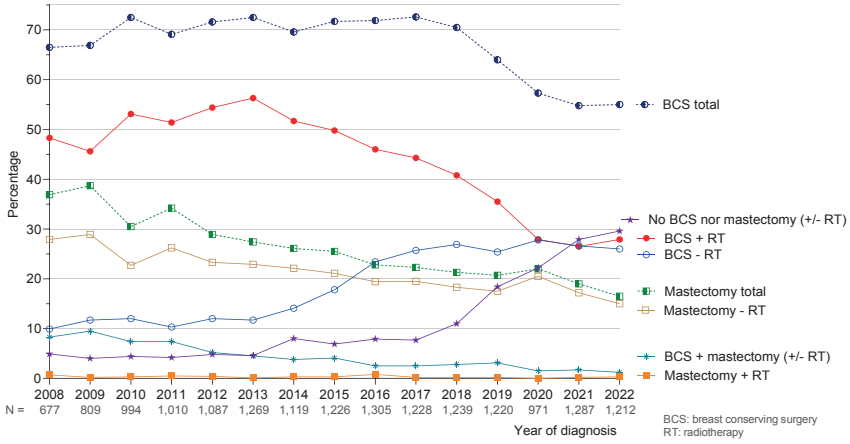| | DCIS grade I-II | | DCIS grade III | |
| | N = 16,653 | | N = 13,534 | |
	n	*(%)*	*n*	*(%)*
Age at time of diagnosis				
<50 years	2,525	(15.2)	1,936	(14.3)
50-75 years	13,121	(78.8)	11,039	(81.6)
>75 years	1,007	(6.0)	559	(4.1)
Year of diagnosis				
2008-2012	4,577	(27.5)	4,258	(31.5)
2013-2017	6,147	(36.9)	5,136	(37.9)
2018-2022	5,929	(35.6)	4,140	(30.6)
Region of residence				
North	1,913	(11.5)	1,765	(13.0)
East	2,866	(17.2)	2,431	(18.0)
South	3,570	(21.4)	2,864	(21.2)
Southwest	3,467	(20.8)	3,178	(23.5)
Northwest	4,837	(29.0)	3,296	(24.4)
Comorbidities assessed [A]	1,953	(11.7)	1,669	(12.3)
No comorbidity in any CCI category	1,349	(69.1)	1,161	(69.6)
Comorbidities in ≥1 CCI category	604	(30.9)	508	(30.4)
Minimal travel time for radiotherapy				
<15 minutes	6,600	(39.6)	4,922	(36.4)
15-30 minutes	8,605	(51.7)	7,368	(54.4)
>30 minutes	1,448	(8.7)	1,244	(9.2)
Diagnosed in a university hospital [B]	1,783	(10.7)	1,040	(7.7)
Radiotherapy as part of the diagnosing hospital	3,941	(23.7)	2,629	(19.4)
Volume in the hospital of diagnosis [C]				
Low volume of diagnoses	2,666	(16.0)	2,260	(16.7)
Intermediate volume of diagnoses	4,836	(29.1)	4,047	(29.9)
High volume of diagnoses	9,145	(54.9)	7,224	(53.4)
DCIS size available [D]	7,611	(45.7)	7,313	(54.0)
≤1 cm	3,194	(42.0)	1,608	(22.0)
>1 – ≤2.5 cm	2,498	(32.8)	2,744	(37.5)
>2.5 cm	1,919	(25.2)	2,961	(40.5)
DCIS palpability available [E]	9,897	(59.4)	8,354	(61.7)
Palpable	1,538	(15.5)	1,348	(16.1)
BCS/mastectomy performed [F]	14,727	(88.4)	13,317	(98.4)
R0-resection	12,445	(84.5)	11,100	(83.4)
R1-resection: focal residual disease	725	(4.9)	704	(5.3)
R1-resection: more than focal residual disease	250	(1.7)	225	(1.7)
Resection margin status unknown	1,307	(8.9)	1,288	(9.7)

Continued

DCIS: ductal carcinoma in-situ; CCI: Charlson Comorbidity Index; BCS: breast conserving surgery

A   Not available for patients diagnosed outside the South region and neither for patients diagnosed in the South region since 2017.

B   Including the single cancer specific hospital in the Netherlands.

C   The one third of hospitals with the lowest number of DCIS diagnoses per year (annual average <18) were classified as low volume, the one third of hospitals with the highest number of DCIS diagnoses per year (annual average >32) were classified as high volume, the other one third of hospitals were classified as intermediate volume.

D   Size of DCIS was available for patients diagnosed since 2013.

E   Palpability of DCIS was available for patients diagnosed in 2011-2019.

F   For 9% of patients who underwent surgery, mainly diagnosed in 2008-2010, information on resection margin status was not available. Focal residual DCIS are into the inked margin in an area of ≤4 mm.

4

In DCIS grade I-II, BCS without radiotherapy increased from ~11% until 2013 to ~26% since 2017 (Figure 1A). The overall proportion of patients receiving BCS was ~72% until 2018, after which a decrease was observed to 55% in 2021-2022 (Figure 1A). Omission of surgery increased from 8% in 2017 to 30% in 2022. Less than 2% of those not operated received radiotherapy. Also, the mastectomy proportion decreased from 37% in 2008 to 18% in 2022. Less than 1% of patients received mastectomy followed by radiotherapy. In DCIS grade III, 61-69% of patients received BCS, often followed by radiotherapy (Figure 1B). Use of BCS without radiotherapy slightly increased from ~3% until 2015 to 7% in 2022. The proportion of mastectomy decreased from 50% in 2008 to 31% in 2022. Use of mastectomy with radiotherapy was limited (<2%), as well as omission of surgery (~2%).

A Grade I-II

B Grade III
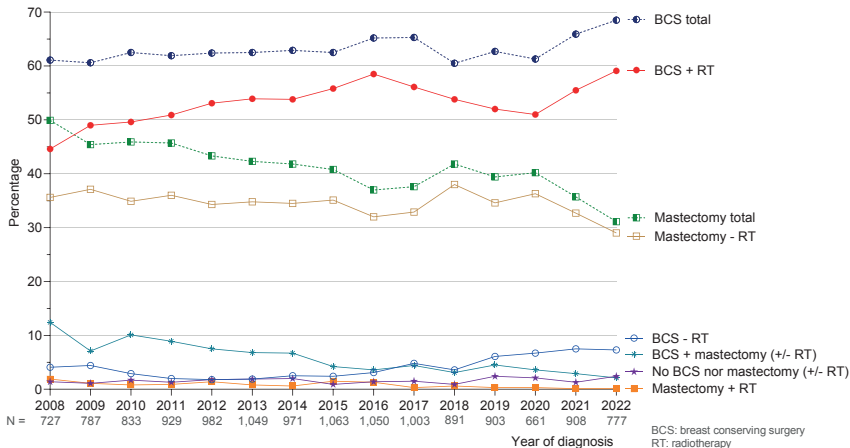
Figure 1. Primary treatment in women diagnosed with DCIS in the Netherlands over the years of diagnosis, stratified for [A] DCIS grade I-II (N = 16,653) and [B] grade III (N = 13,534)

Women at screening ages, compared to younger and older women, more often received radiotherapy. In DCIS grade I-II, use of BCS with radiotherapy varied from 44% to 52% in women aged 50-75 years (Figure 2A). In DCIS grade III, BCS with radiotherapy was administered in 56% to 61% of women aged 50-75 years (Figure 2B). Mastectomy was more common in younger women, while omission of surgery and omission of radiotherapy following BCS was more common with increasing age.
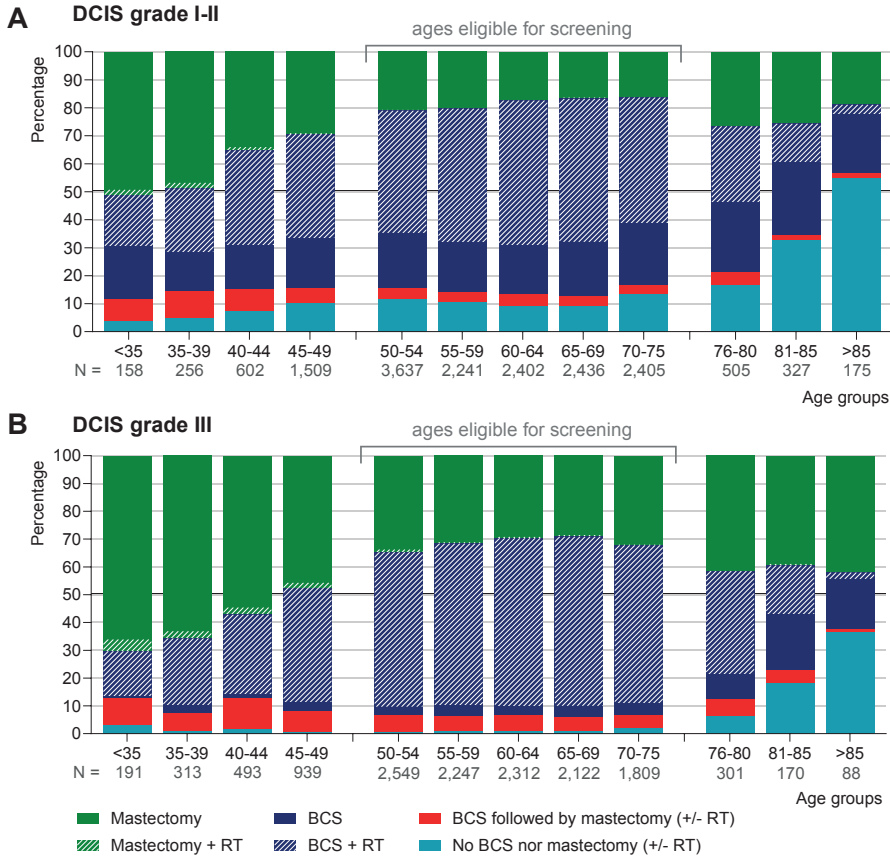
Figure 2. Primary treatment according to age groups in women diagnosed with [A] DCIS grade I-II (N = 16,653) and [B] DCIS grade III (N = 13,534)

In DCIS grade I-II, age, period of diagnosis, travel time for radiotherapy, lesion size and resection margin status were statistically significant associated with administration of radiotherapy after BCS (Table 2). More specifically, women aged <50 (OR:0.86, 95%CI:0.75-0.99) and >75 (OR:0.30, 95%CI:0.24-0.37) were less likely to receive radiotherapy than those aged 50-75, while those with >30 compared to <15 minutes travel time for radiotherapy, DCIS sized >1 vs ≤1 cm, and a R1 versus R0-resection were more likely to receive radiotherapy. Decreased use of radiotherapy after BCS over time was demonstrated by ORs of 0.55 (95%CI: 0.45-0.68) for DCIS grade I-II diagnoses in 2013-2017 and 0.24 (95%CI: 0.20-0.30) for 2018-2022, both compared to 2008-2012.

In DCIS grade III, age, period of diagnosis, travel time for radiotherapy, type of hospital, and lesion size were associated with post-BCS radiotherapy (Table 2).

Women aged >75 were less likely to receive radiotherapy than those aged 50-75 (OR:0.12, 95%CI:0.09-0.16), as well as those diagnosed in 2018-2022 compared to 2008-2012 (OR:0.50, 95%CI:0.38-0.66) and those who underwent BCS in a university compared to no-university hospital. Women with 15-30 compared to <15 minutes of travel time for radiotherapy were more likely to receive post-BCS radiotherapy, as well as those with lesions sized >1 versus ≤1 cm.

Table 2. Adjusted odds ratios (OR) of receiving BCT versus BCS without radiotherapy (RT), stratified for women diagnosed with DCIS grade I-II (N=10,489) and grade III (N=7,747) in the Netherlands

	DCIS grade I-II		DCIS grade III	
	BCT, N = 7,269		BCT, N = 7,219	
	BCS without RT, N = 3,220		BCS without RT, N = 528	
	OR [A]	(95%CI)	OR [B]	(95%CI)
Age at time of diagnosis				
< 50 years	**0.86**	**(0.75-0.99)**	0.93	(0.66-1.30)
50-75 years	Reference		Reference	
> 75 years	**0.30**	**(0.24-0.37)**	**0.12**	**(0.09-0.16)**
Year of diagnosis				
2008-2012	Reference		Reference	
2013-2017	**0.55**	**(0.45-0.68)**	1.07	(0.80-1.44)
2018-2022	**0.24**	**(0.20-0.30)**	**0.50**	**(0.38-0.66)**
Region of residence				
North	Reference		Reference	
East	1.11	(0.82-1.51)	1.14	(0.75-1.72)
South	1.29	(0.93-1.78)	0.75	(0.51-1.10)
Southwest	1.17	(0.85-1.60)	0.87	(0.59-1.27)
Northwest	1.15	(0.85-1.54)	1.01	(0.69-1.48)
Comorbidities [C]				
No comorbidity in any CCI category	Reference		Reference	
Comorbidity in ≥1 CCI component	0.96	(0.70-1.34)	0.84	(0.45-1.57)
Minimal travel time for radiotherapy				
< 15 minutes	Reference		Reference	
15-30 minutes	1.06	(0.95-1.18)	**1.25**	**(1.02-1.54)**
> 30 minutes	**1.24**	**(1.01-1.51)**	0.92	(0.64-1.32)
Hospital of surgery				
Non-university	Reference		Reference	
University [D]	0.87	(0.61-1.25)	**0.48**	**(0.32-0.70)**
RT as part of the hospital of surgery				
No	Reference		Reference	
Yes	0.98	(0.75-1.29)	1.03	(0.74-1.45)
Volume in the hospital of surgery				
Low volume of diagnoses	Reference		Reference	
Intermediate volume of diagnoses	0.78	(0.60-1.01)	1.01	(0.72-1.41)
High volume of diagnoses	0.83	(0.64-1.07)	0.92	(0.67-1.26)

Continued

| | DCIS grade I-II | | DCIS grade III | |
| | BCT, N = 7,269 | | BCT, N = 7,219 | |
	BCS without RT, N = 3,220		BCS without RT, N = 528	
	OR [A]	(95%CI)	OR [B]	(95%CI)
DCIS size [E]				
≤1 cm	Reference		Reference	
>1 – ≤2.5 cm	**2.87**	**(2.40-3.42)**	**1.81**	**(1.38-2.38)**
>2.5 cm	**4.63**	**(3.61-5.93)**	**2.34**	**(1.64-3.34)**
DCIS palpability [F]				
Not palpable	Reference		Reference	
Palpable	0.86	(0.69-1.06)	0.81	(0.54-1.21)
Resection margin status				
R0 resection	Reference		Reference	
R1 resection: (more than) focal residual disease	**2.08**	**(1.72-2.52)**	0.88	(0.65-1.20)

OR: odds ratio, BCT: breast conserving therapy, BCS: breast conserving surgery, RT: radiotherapy, DCIS: ductal carcinoma in-situ, 95%CI: 95%% confidence interval, CCI: Charlson Comorbidity Index; values in bold are statistically significant

A   Multilevel logistic regression models with both a random intercept and random effect were applied for year of diagnosis and travel time. The analysis on year of diagnosis was not adjusted, as none of the variables fulfilled the criterium for inclusion in the adjustment set. The analysis on age was adjusted for year of diagnosis and resection margin status. The analysis on region was adjusted for volume of diagnosis and resection margin status. The analysis on comorbidities was adjusted for age, year of diagnosis, region and resection margin status. The analysis on travel time was adjusted for year of diagnosis. The analysis on type of hospital was adjusted for year of diagnosis, travel time and volume of diagnosis. The analysis on radiotherapy in the hospital was adjusted for year of diagnosis and travel time. The analysis on volume of diagnoses was adjusted for travel time. The analysis on DCIS size was adjusted for year of diagnosis and age. The analyses on DCIS palpability and resection margin status were adjusted for age. NB. Comorbidities, DCIS size and DCIS palpability were not included in adjustment sets, considering their limited availability. The analysis on type of hospital was not adjusted for a radiotherapy department in the hospital, as this was considered a basic component of university hospitals.

B   A multilevel logistic regression model with both a random intercept and random effect was applied for year of diagnosis. The analyses for age, travel time and type of hospital were adjusted for year of diagnosis and resection margin status. The analyses for year of diagnosis was adjusted for resection margin status. The analyses for region and resection margin status were not adjusted, as none of the variables fulfilled the criterium for inclusion in the adjustment sets. The analysis for comorbidities was adjusted for age and resection margin status. The analysis for radiotherapy in the hospital was adjusted for type of hospital. The analysis for volume of diagnoses was adjusted for year of diagnosis and type of hospital. The analysis for DCIS size was adjusted for year of diagnosis and age. The analysis for DCIS palpability was adjusted for age. NB. Comorbidities, DCIS size and DCIS palpability were not included in adjustment sets, considering their limited availability. The analysis on type of hospital was not adjusted for a radiotherapy department in the hospital, as this was considered a basic component of university hospitals.

C   Not available for patients diagnosed outside the South region and neither for patients diagnosed in the South region since 2017.

D   Including the single cancer specific hospital in the Netherlands.

E   Size of DCIS was available for patients diagnosed since 2013.

F   Palpability of DCIS was available for patients diagnosed in 2011-2019.

In women who underwent BCS and radiotherapy, use of a boost decreased over time. In DCIS grade I-II, WBI with boost decreased from 40% in 2011 to 11% in 2022, coinciding increased use of WBI without boost in 2011-2018 (55%-72%) and increased use of PBI in 2019-2022 (5%-27%) (Figure 3.1A). In DCIS grade III, WBI with boost decreased in recent years from ~53% in 2011-2019 to 33% in 2022 (Figure 3.2A). PBI was limited in DCIS grade III (~1%).

Boost irradiation following BCS diminished with increasing age in women aged ≤75. In DCIS grade I-II, use of WBI with boost varied from 60% in ages <40 to 24% in ages 70-75 (Figure 3.1B). In women aged >75, 28% received a boost. PBI in DCIS grade I-II was administered in ~5% of women aged ≥50. In DCIS grade III, WBI with boost varied from 68% in ages <40 to 36% in ages 70-75 (Figure 3.2B). In women aged >75, 37% received a boost.

In DCIS grade I-II, age, period of diagnosis, hospital volume, lesion size and resection margin status were statistically significant associated with boost irradiation in post-BCS WBI (Table 3). Women aged <50 compared to 50-75 were more likely to receive a boost (OR:2.96, 95%CI:2.31-3.78), as well as women with DCIS sized >1 versus ≤1 cm, and those with a R1- compared to R0-resection (OR:19.97, 95%CI:12.88-30.96). The observed trend over time was evidenced by ORs of 0.60 (95%CI: 0.45-0.81) for diagnoses in 2015-2018 and 0.26 (95%CI: 0.19-0.37) for 2019-2022, both compared to 2011-2014.

In DCIS grade III, age, period of diagnosis, presence of a radiotherapy department, lesion size, and resection margin status were associated with use of WBI with boost versus without (Table 3). Women aged <50 were more likely to receive a boost (OR:2.07, 95%CI:1.65-2.60), while those aged >75 were less likely (OR:0.38, 95%CI:0.25-0.60), both compared to those aged 50-75. Being diagnosed in 2019-2022 compared to 2011-2014 was associated with less boost irradiation (OR:0.52, 95%CI:0.38-0.69), while BCS performed in a hospital with radiotherapy department and DCIS size (>1 compared to ≤1 cm) were associated with more use of a boost. A R1- compared to R0-resection was strongly associated with boost irradiation (OR:15.01, 95%CI:10.54-21.38).
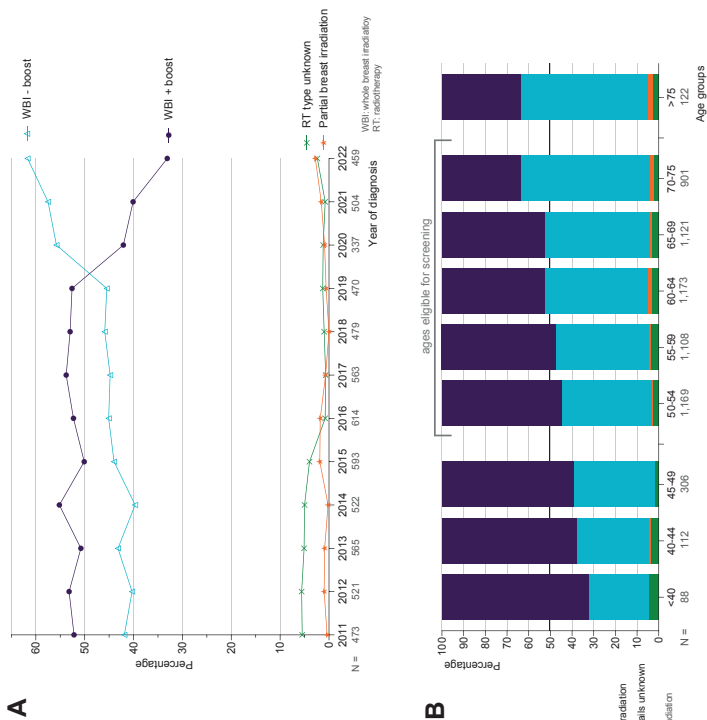
Figure 3. Details on radiotherapy administered in women diagnosed with DCIS in 2011-2022 who underwent BCS and radiotherapy, stratified for [1] DCIS grade I-II (N = 6,048) and [2] grade III (N = 6,100) and presented over [A] the years of diagnosis and [B] according to age groups

Table 3. Adjusted odds ratios (OR) of receiving WBI with versus without boost irradiation in BCT, stratified for women diagnosed with DCIS grade I-II (N=5,562) and grade III (N=5,857) in 2011-2022 in the Netherlands

	DCIS grade I-II		DCIS grade III	
	Post-BCS WBI with boost, N = 1,914 without boost, N = 3,648		Post-BCS WBI with boost, N = 3,016 without boost, N = 2,841	
	OR [A]	(95%CI)	OR [B]	(95%CI)
Age at time of diagnosis				
< 50 years	**2.96**	**(2.31-3.78)**	**2.07**	**(1.65-2.60)**
50-75 years	Reference		Reference	
> 75 years	0.72	(0.45-1.17)	**0.38**	**(0.25-0.60)**
Year of diagnosis				
2011-2014	Reference		Reference	
2015-2018	**0.60**	**(0.45-0.81)**	0.89	(0.67-1.18)
2019-2022	**0.26**	**(0.19-0.37)**	**0.52**	**(0.38-0.69)**
Region of residence				
North	Reference		Reference	
East	1.00	(0.61-1.63)	0.96	(0.57-1.62)
South	0.82	(0.48-1.40)	0.67	(0.36-1.24)
Southwest	0.78	(0.46-1.33)	0.81	(0.44-1.46)
Northwest	1.51	(0.93-2.47)	1.41	(0.83-2.39)
Comorbidities [C]				
No comorbidity in any CCI category	Reference		Reference	
Comorbidity in ≥1 CCI component	0.74	(0.49-1.14)	0.80	(0.53-1.20)
Minimal travel time for radiotherapy				
< 15 minutes	Reference		Reference	
15-30 minutes	1.07	(0.91-1.24)	1.11	(0.96-1.28)
> 30 minutes	0.99	(0.74-1.32)	1.11	(0.85-1.46)
Hospital of surgery				
Non-university	Reference		Reference	
University [D]	0.74	(0.41-1.35)	1.01	(0.43-2.36)
RT as part of the hospital of surgery				
No	Reference		Reference	
Yes	1.27	(0.66-2.46)	**2.48**	**(1.07-5.79)**
Volume in the hospital of surgery				
Low volume of diagnoses	Reference		Reference	
Intermediate volume of diagnoses	**0.55**	**(0.34-0.89)**	0.56	(0.31-1.04)
High volume of diagnoses	0.70	(0.44-1.11)	0.97	(0.53-1.77)
DCIS size [E]				
≤1 cm	Reference		Reference	
>1 – ≤2.5 cm	**1.53**	**(1.25-1.86)**	**1.57**	**(1.32-1.87)**
>2.5 cm	**2.56**	**(2.01-3.26)**	**2.06**	**(1.67-2.52)**
DCIS palpability [F]				
Not palpable	Reference		Reference	
Palpable	1.15	(0.93-1.42)	1.09	(0.85-1.39)

Continued

	DCIS grade I-II		DCIS grade III	
	Post-BCS WBI		Post-BCS WBI	
	with boost, N = 1,914		with boost, N = 3,016	
	without boost, N = 3,648		without boost, N = 2,841	
	OR [A]	(95%CI)	OR [B]	(95%CI)
Resection margin status				
R0 resection	Reference		Reference	
R1 resection: (more than) focal residual disease	**19.97**	**(12.88-30.96)**	**15.01**	**(10.54-21.38)**

OR: odds ratio, BCS: breast conserving surgery, WBI: whole breast irradiation, DCIS: ductal carcinoma in-situ, 95%CI: 95%-confidence interval, CCI: Charlson Comorbidity Index; RT: radiotherapy, values in bold are statistically significant

A Multilevel logistic regression models with both a random intercept and random effect were applied for year of diagnosis, age and resection margin status. The analyses for age and travel time were adjusted for year of diagnosis and resection margin status. The analysis for year of diagnosis was adjusted for resection margin status. The analysis for region was adjusted for year of diagnosis, age, resection margin status and volume of diagnosis. The analysis for comorbidities was adjusted for age and resection margin status. The analysis for type of hospital was adjusted for region, resection margin status and volume of diagnosis. The analysis for radiotherapy in the hospital was adjusted for resection margin status and type of hospital. The analyses for volume of diagnosis were adjusted for year of diagnosis, region and resection margin status. The analysis for DCIS size was adjusted for year of diagnosis. The analysis for DCIS palpability was adjusted for age. The analysis for resection margin status was adjusted for year of diagnosis and age. NB. Comorbidities, DCIS size and DCIS palpability were not included in adjustment sets, considering their limited availability. The analysis on type of hospital was not adjusted for a radiotherapy department in the hospital, as this was considered a basic component of university hospitals.

B A multilevel logistic regression model with both a random intercept and random effect was applied for year of diagnosis. The analysis on age, year of diagnosis and region was adjusted for resection margin status. The analyses on comorbidities and DCIS palpability were adjusted for age. The analysis on travel time was not adjusted, as none of the variables fulfilled the criterium for inclusion in the adjustment set. The analysis on type of hospital was adjusted for region and resection margin status. The analysis on radiotherapy in the hospital of diagnosis was adjusted for type of hospital. The analysis on volume of diagnosis was adjusted for year of diagnosis and region. The analyses on DCIS size and resection margin status were adjusted for year of diagnosis. NB. Comorbidities, DCIS size and DCIS palpability were not included in adjustment sets, considering their limited availability. The analysis on type of hospital was not adjusted for a radiotherapy department in the hospital, as this was considered a basic component of university hospitals.

C Not available for patients diagnosed outside the South region and neither for patients diagnosed in the South since 2017.

D Including the single cancer specific hospital in the Netherlands.

E Size of DCIS was available for patients diagnosed since 2013.

F Palpability of DCIS was available for patients diagnosed until 2019.

DISCUSSION

This nationwide study demonstrates decreased use of surgery and decreased use of radiotherapy following BCS in DCIS grade I-II. Also, boost irradiation became increasingly omitted and increased use of PBI was observed, both in DCIS grade I-II and grade III. Older patients most often had surgery and post-BCS radiotherapy omitted and most often received WBI without boost and PBI.

Omission of surgery and/or radiotherapy

DCIS traditionally has been managed with BCS followed by radiotherapy or mastectomy [13,33]. Various studies aim to identify subsets of women with low-risk DCIS in whom both surgery and radiotherapy or radiotherapy following BCS can be omitted, aiming to prevent the harms of (over)treatment [20-25]. Low grade-DCIS and older age have been associated with a low-risk of (invasive) recurrence [16,24], which is reflected in the observed omission of surgery and post-BCS radiotherapy mainly in women with DCIS grade I-II and in women aged >75. Also in the US, older patients and those with low/intermediate-grade DCIS were found less likely to receive radiotherapy following BCS [34]. In DCIS grade III, we observed a slightly increasing proportion of older women who underwent BCS without radiotherapy in the most recent years. Nevertheless, BCS with radiotherapy remained the mainstay of DCIS grade III management. This is in line with recent European treatment guidelines mentioning post-BCS radiotherapy omission an option only in women with low/intermediate grade DCIS without high-risk features for (invasive) recurrences [7]: residual disease and larger DCIS [16]. We likewise showed that women with DCIS grade I-II less likely had radiotherapy omitted following a R1 versus R0-resection, and that the probability of receiving post-BCS radiotherapy increased with increasing lesion size (both in DCIS grade I-II and grade III).

In DCIS grade I-II, we found ages <50 versus 50-75 to have a lower probability of receiving radiotherapy following BCS. However, this does not reflect treatment de-intensification in younger patients, as women aged <50 more often received mastectomy instead of BCS with radiotherapy [35]. High rates of mastectomy (73%) in young women diagnosed with DCIS were also observed in the US [36]. In our study, increased travel time for radiotherapy (both in DCIS grade I-II and III) and undergoing BCS in a non-university hospital (only in grade III) were

associated with a higher probability of post-BCS radiotherapy. These associations may reflect (implementation differences in) shared-decision making.

De-intensification of the radiotherapy treatment following BCS

Radiotherapy following BCS can be de-intensified by omitting a boost or providing PBI instead of WBI [6,7]. Awaiting long-term outcomes, PBI is only considered an option in women with low-risk DCIS [6,7]. We indeed observed PBI use mainly in women aged ≥50 bearing DCIS grade I-II. Uniform indications for administering a boost in DCIS treatment in the Netherlands were lacking [29] until recently [37]. Nevertheless, regional differences were not found in administering WBI with or without a boost. We did find patient and disease characteristics implying a high-risk of poor prognosis [16,24], including young age, irradicality, and larger DCIS lesions, to be associated with use of a boost. These findings are largely in line with the nationwide consensus on boost indications in DCIS treatment, established in 2020 by the Dutch Association of Radiation Oncology's nationwide working group on breast tumors. Irradicality is an unequivocal indication for a boost in the consensus document, while boost irradiation should be decided upon through shared decision-making in case of age ≤40 or DCIS grade III [37]. Increased application of shared decision-making on boost irradiation may explain why we observed decreased use of boost irradiation, also in DCIS III in the most recent years.

Novel insights

An increasing tendency to forego radiotherapy was previously reported in low-grade DCIS in 2008-2018 [13], which we showed to continue until 2020 and remain stable since. In addition, in DCIS grade I-II, we observed omission of surgery in older patients, decreased use of boost irradiation and increased use of PBI, all previously not described. In 2011-2016, another Dutch study found utilization of boost irradiation being stable over time, with a higher probably of receiving a boost in high-risk patients (among others: DCIS grade III) [29]. We also found high-risk patients to be more likely to receive a boost, but also observed decreasing use of boost irradiation – even in DCIS grade III. Furthermore, in DCIS grade III, we noted slightly increasing omission of radiotherapy since 2018, mainly in older patients, which was previously not observed [13]. Also, our study provided insight in treatment variation between screening ages and younger

and older age, while the previous report on post-BCS radiotherapy use included only screenings ages [13], and we provided insights in varying administration of post-BCS radiotherapy, which previously remained uninvestigated.

Our study period included the COVID-19 pandemic, in contrary to previous studies. Due to the pandemic, the breast cancer screening program in the Netherlands was discontinued for four months in 2020 [39], which resulted in less DCIS diagnoses compared to prior and subsequent years. Moreover, surgery in (low/intermediate-grade) DCIS has been delayed in order to ease the pressure on the hospitals posed by the pandemic [40]. However, the treatment patterns that we observed in 2020, did not differ from demonstrated trends over time.

Strengths and limitations

This study provides a comprehensive nationwide overview of radiotherapy de-intensification in DCIS treatment in the Netherlands. We used data up to the most recent year available from a population-based registry, to provide novel insights in DCIS treatment patterns in the Netherlands. Limitations of our study include being unable to evaluate changes in the radiotherapy schemes, as information on dosage and fractionation were not available. Also, comorbidities, DCIS size and palpability were limited available and performance status lacked, for which the analyses could consequently not be adjusted. Particularly, our finding of older women receiving less intensive treatment may therefore reflect frailty instead of merely calendar age. Also, more frequent use of (boost) radiotherapy found in high-risk features may reflect DCIS size/ palpability instead of solely the respective high-risk feature.

Conclusions

This nationwide study reporting on 2008-2022 showed that de-intensification of DCIS treatment is clearly ongoing in the Netherlands. We observed that surgery and post-BCS radiotherapy were increasingly omitted in older patients with DCIS grade I-II. Also, radiotherapy following BCS in DCIS grade I-II de-intensified by decreased use of a boost and increased PBI application. De-intensification of DCIS grade III treatment was observed by slightly increased use of BCS without radiotherapy in older women, and by decreased boost use. Women at higher risk of (invasive) local recurrence least often had post-

BCS radiotherapy or boost irradiation omitted, which reflects the efforts in identifying subsets of women eligible for treatment de-intensification. While hospital-characteristics were associated with post-BCS (boost) radiotherapy, no regional differences were found.

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Supplementary Figure 1. Classification of geographical regions in the Netherlands
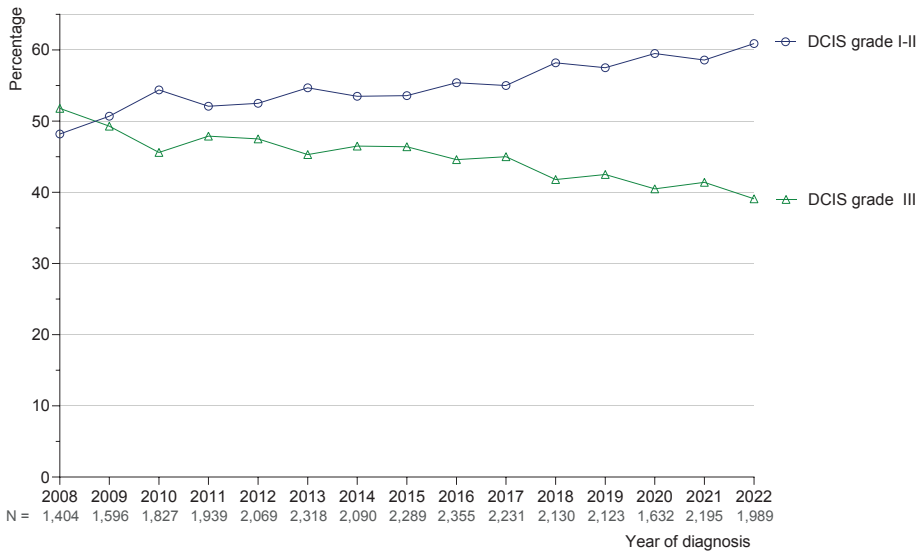
Supplementary Figure 2. Proportion of DCIS grade I-II and grade III diagnoses over time

Supplementary Table 1. Categorization of comorbidities

Categories used in the current study	Original Charlson Comorbidity Index categories
● Previous malignancy (M0/M+)	● Tumor without malignancy
	● Metastatic malignancy
	● Lymphoma
	● Leukemia
● Myocardial infarction	● Myocardial infarction
● Congestive heart failure	● Congestive heart failure
● Peripheral vascular disease	● Peripheral vascular disease
● Cerebrovascular disease / hemiplegia	● Cerebrovascular disease
	● Hemiplegia
● Chronic pulmonary disease	● Chronic pulmonary disease
● Diabetes Mellitus	● Diabetes Mellitus
	● Diabetes Mellitus with end organ damage
● Renal disease	● Moderate / severe renal disease
● Liver disease	● Mild liver disease
	● Moderate / severe liver disease
● Ulcer disease	● Ulcer disease
● Dementia	● Dementia
● Rheumatoid Arthritis	● Connective tissue disease
● HIV	● AIDS

Comorbidities which could not be included in the above categories were disregarded

Categories were not assigned weights

CHAPTER

5

Total radiotherapy in
invasive M0 breast cancer

RADIOTHERAPY TRENDS AND VARIATIONS IN INVASIVE NON-METASTATIC BREAST CANCER TREATMENT IN THE NETHERLANDS: A NATIONWIDE OVERVIEW FROM 2008 TO 2019

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Submitted.

ABSTRACT

Purpose:

This nationwide study provides overview of trends and variations in radiotherapy use as part of multimodal treatment of invasive non-metastatic breast cancer in the Netherlands in 2008-2019.

Methods:

Women with invasive non-metastatic breast cancer were selected from the population-based Netherlands Cancer Registry. Treatments were presented over time. Factors associated with (1)boost irradiation in breast-conserving therapy (BCT) and (2)regional radiotherapy instead of axillary lymph node dissection (ALND) in N+ disease were identified using multilevel logistic regression analyses.

Results:

Radiotherapy use increased from 61% (2008) to 70% (2016), caused by BCT instead of mastectomy, increased post-mastectomy radiotherapy, and increased regional radiotherapy (32% in 2011-61% in 2019) instead of ALND in N+ disease. Omission of radiotherapy after breast-conserving surgery (BCS) in 2016-2019 (4-9%, respectively), mainly in elderly, decreased overall radiotherapy use to 67%. Radiotherapy treatment further de-escalated by decreased boost irradiation in BCT (66%, 2011-37%, 2019) and partial (1%, 2011-6%, 2019) instead of whole breast irradiation following BCS. Boost irradiation was associated with high-risk features: younger age (OR>75 vs <50:0.04, 95%CI:0.03-0.05), higher grade (OR grade III vs I:11.46, 95%CI:9.90-13.26) and residual disease (OR focal residual vs R0-resection:28.08, 95%CI:23.07-34.17). Variation across the country was found for both boost irradiation use, and regional radiotherapy instead of ALND (OR Southwest vs North:0.55, 95%CI:0.37-0.80).

Conclusions:

Overall radiotherapy use increased in 2008-2016, while a decreasing trend was observed after 2016, caused by post-BCS radiotherapy omission. Boost irradiation in BCT became omitted in low-risk patients and regional radiotherapy use increased as an alternative for ALND in N+ disease.

INTRODUCTION

Breast cancer (BC) accounts for one fourth of all cancer diagnoses in women worldwide[1]. In the Netherlands, ~15,000 women are diagnosed with invasive non-metastatic BC annually[2], most commonly at screening ages: 50-75 years[3].

Radiotherapy is a key modality in invasive non-metastatic BC treatment. Traditionally, breast-conserving therapy (BCT) includes breast-conserving surgery (BCS) followed by whole breast irradiation (WBI)[4-7] to prevent recurrences and ultimately BC deaths[8]. Furthermore, a tumor bed radiation boost can be administered[4-7] to further reduce the local recurrence risk[9]. The increased incidence of early BC[10] and improved BC prognosis[10,11] provided opportunities for personalized treatment and shared decision-making. Consequently, radiotherapy use following BCS de-escalated in subsets of patients, aiming to prevent treatment-related toxicity[12]. Nowadays, partial breast irradiation (PBI) instead of WBI is considered in patients at low-risk of local recurrence[5-7,13-18] and even BCS without radiotherapy is considered in very low-risk patients (i.e. older age, luminal A subtype, BC measuring <2cm, free resection margins)[5,6,19-22]. Furthermore, boost irradiation in BCT is increasingly omitted considering the small absolute local recurrence risk reduction, the lack of benefit in overall survival and increased rates of fibrosis and deterioration of cosmetic result[4-7,9,23-25]. Radiotherapy following mastectomy is traditionally administered in high-risk patients[4-7] to improve recurrence-free and overall survival[26,27]. Nowadays, postmastectomy radiotherapy (PMRT) is also considered in intermediate-risk patients[5,6,28]. In patients with limited sentinel node involvement, regardless of local surgery, regional radiotherapy is considered as alternative to axillary lymph node dissection (ALND)[4-7], since comparable locoregional recurrence rates and overall survival were reported for ALND and regional radiotherapy without ALND[29-31].

Previously, overall radiotherapy use in invasive non-metastatic BC was noted to increase over time[10,32,33], while boost irradiation in BCT decreased[34]. However, a recent overview also addressing PBI, regional radiotherapy and variations in radiotherapy use, as well as radiotherapy use including boost irradiation since 2016 is lacking. Our study aims to provide this comprehensive overview of trends and variations in the nationwide radiotherapy use as part of multimodal treatment of invasive non-metastatic BC in the Netherlands from 2008 to 2019.

METHODS

Women diagnosed with invasive non-metastatic BC in 2008-2019 were selected from the Netherlands Cancer Registry (NCR). The population-based NCR contains patient-, tumor- and treatment-related information on all patients diagnosed with cancer in the Netherlands. Trained data managers extracted these data from hospitals' medical records. TNM6 (2008-2009), TNM7 (2010-2016), and TNM8 (2017-2019) were used for staging. The Bloom-Richardson system was used for grading. Patients living, diagnosed, or treated abroad, and those diagnosed during autopsy were excluded.

Characteristics of patients, hospitals of diagnosis and disease, were presented stratified for women aged <50, 50-75, and >75, based on the screening ages. To classify patients' region of residence, we divided the Netherlands into five geographical regions (Supplementary Figure 1); each including ≥3 radiotherapy facilities and ≥11 hospitals (≥1 university hospital). Travel time to a radiotherapy facility (<15/15-30/>30 minutes) was calculated as a one-way trip by car using the 2013-GEODAN drive time matrix[35] and postal codes of patients' residence and nearest radiotherapy facility. We classified hospitals of diagnosis according to presence of a radiotherapy department (excluding radiotherapy facilities of other institutes located in the same building), and by tertiles as either low-volume hospital (<1,451 primary non-metastatic BC diagnoses in the study period), intermediate-volume (1,451-2,646 diagnoses), or high-volume (>2,646 diagnoses).

Information on variables limited available, including performance status and comorbidities at the time of BC diagnosis, were presented in the supplementary. Comorbidities were categorized based on the Charlson Comorbidity Index (Supplementary Table 1).

Primary treatment was presented over time and according to age groups. Before 2011, radiotherapy use was only available as yes/no. Since 2011, details on radiotherapy were available and presented stratified for women who underwent BCT: PBI/WBI with boost/WBI without boost, and mastectomy: PMRT with boost/PMRT without boost. Use of regional radiotherapy (available from 2011) and ALND was presented for women with (y)pN+ and/or cN+ disease. Visualizations according to age groups were stratified for the early and more recent years, to assess age groups with changed treatment patterns by temporal trends.

Multilevel logistic regression analyses, accounting for nesting of patients within hospitals, were applied to identify factors associated with (1)post-BCS WBI with boost versus without, and (2)regional radiotherapy versus ALND in women with (y)pN+ and/or cN+ disease. Women treated with BCS followed by mastectomy were excluded from analysis (1) on WBI with boost versus without. Women who received both regional radiotherapy and ALND were excluded from analysis (2) on regional treatment. The analyses were executed with both a random effect and random intercept for the various hospitals when the corrected Akaike Information Criterion (AICc) improved compared to analyses with only a random intercept. For each association investigated, factors were selected for adjustment if univariable inclusion resulted in ≥5% change in the odds ratio (OR) of interest compared to the unadjusted OR from multilevel analysis. Ninety-five percent confidence intervals (95%CI) were calculated. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, US).

RESULTS

Between January 1st, 2008, and December 31st, 2019, 176,292 women were diagnosed with non-metastatic BC: 20% aged <50, 64% aged 50-75, and 16% aged >75. Distribution between regions and hospital characteristics were largely similar across the various age groups (Table 1). Patients at ages eligible for screening (50-75 years) were diagnosed with less advanced disease and had more often a sentinel lymph node biopsy (SLNB) performed (82%) compared to those aged <50 (75%) and >75 (45%). Patients aged <50 had the best performance status (89% had performance status 0, indicating being fully functional). For patients aged >75, comorbidities were most often noted (Supplementary Table 2).

Table 1. Patient, disease, and hospital characteristics, for women diagnosed with invasive non-metastatic breast cancer in the Netherlands (N=176,292), stratified for ages <50, 50-75 and >75 years

	Aged <50 years		Aged 50-75 years		Aged >75 years	
	N = 35,540		N = 112,255		N = 28,497	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*
Median age at time of diagnosis (p25, p75)	44.0	(40.0-47.0)	63.0	(56.0-68.0)	83.0	(79.0-87.0)
Year of diagnosis						
2008-2010	9,037	(25.4)	25,104	(22.4)	6,571	(23.1)
2011-2013	9,094	(25.6)	28,054	(25.0)	7,032	(24.7)
2014-2016	8,689	(24.4)	29,372	(26.2)	7,146	(25.1)
2017-2019	8,720	(24.5)	29,725	(26.5)	7,748	(27.2)
Region of residence						
North	4,318	(12.1)	14,763	(13.2)	3,726	(13.1)
East	6,037	(17.0)	19,550	(17.4)	5,015	(17.6)
South	7,496	(21.1)	25,190	(22.4)	6,345	(22.3)
Southwest	7,928	(22.3)	24,750	(22.0)	6,637	(23.3)
Northwest	9,761	(27.5)	28,002	(24.9)	6,774	(23.8)
Grade						
Grade I	5,387	(15.2)	28,772	(25.6)	4,451	(15.6)
Grade II	13,483	(37.9)	50,679	(45.1)	10,737	(37.7)
Grade III	11,868	(33.4)	24,058	(21.4)	5,750	(20.2)
Unknown	4,802	(13.5)	8,746	(7.8)	7,559	(26.5)
Clinical T-stage						
cTis	662	(1.9)	2,607	(2.3)	184	(0.6)
cT0	163	(0.5)	390	(0.3)	56	(0.2)
cT1	16,370	(46.1)	71,467	(63.7)	10,905	(38.3)
cT2	13,720	(38.6)	28,106	(25.0)	13,002	(45.6)
cT3	3,029	(8.5)	4,090	(3.6)	1,614	(5.7)
cT4	670	(1.9)	1,938	(1.7)	2,271	(8.0)
cTX	926	(2.6)	3,657	(3.3)	465	(1.6)
Pathological T-stage						
(y)pT0	3,248	(9.1)	3,060	(2.7)	88	(0.3)
(y)pT1	19,449	(54.7)	77,510	(69.0)	7,866	(27.6)
(y)pT2	9,861	(27.7)	25,096	(22.4)	8,881	(31.2)
(y)pT3	1,376	(3.9)	2,733	(2.4)	1,014	(3.6)
(y)pT4	112	(0.3)	486	(0.4)	548	(1.9)
(y)pTX/not classified	1,494	(4.2)	3,370	(3.0)	10,100	(35.4)
ALND performed	10,498	(29.5)	20,931	(18.6)	4,970	(17.4)
SLNB performed [A]	26,595	(74.8)	91,907	(81.9)	12,913	(45.3)

Continued

	Aged <50 years		Aged 50-75 years		Aged >75 years	
	N = 35,540		N = 112,255		N = 28,497	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*
N-stage [B]						
cN0 → (y)pN0	18,291	(51.5)	72,790	(64.8)	10,209	(35.8)
cN0 → (y)pN+	6,782	(19.1)	18,947	(16.9)	3,627	(12.7)
cN0 → (y)pNX/not classified	537	(1.5)	3,896	(3.5)	8,210	(28.8)
cN+ → (y)pN0	2,480	(7.0)	2,693	(2.4)	227	(0.8)
cN+ → (y)pN+	6,561	(18.5)	11,570	(10.3)	2,927	(10.3)
cN+ → (y)pNX/not classified	399	(1.1)	1,091	(1.0)	2,586	(9.1)
cNX → (y)pN0	233	(0.7)	564	(0.5)	119	(0.4)
cNX → (y)pN+	221	(0.6)	471	(0.4)	105	(0.4)
cNX → (y)pNX/not classified	36	(0.1)	233	(0.2)	487	(1.7)
BCS/mastectomy performed [C]	35,069	(98.7)	110,080	(98.1)	18,459	(64.8)
R0-resection	29,169	(83.2)	95,496	(86.8)	16,061	(87.0)
R1-resection: focal residual tumor	1,204	(3.4)	4,169	(3.8)	657	(3.6)
R1-resection: more than focal residual tumor	355	(1.0)	977	(0.9)	232	(1.3)
Resection margin status unknown	4,341	(12.4)	9,438	(8.6)	1,509	(8.2)
Diagnosed in a university hospital [D]	2,851	(8.0)	8,455	(7.5)	1,438	(5.0)
Radiotherapy in the diagnosing hospital's organization	7,144	(20.1)	21,822	(19.4)	4,999	(17.5)
Volume of diagnoses in the hospital of diagnosis						
Low volume of diagnoses	5,387	(15.2)	17,082	(15.2)	4,004	(14.1)
Intermediate volume of diagnoses	9,920	(27.9)	32,466	(28.9)	8,408	(29.5)
High volume of diagnoses	20,224	(56.9)	62,700	(55.9)	16,078	(56.4)

p25: 25th percentile, p75: 75th percentile; T: tumor, N: lymph node; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy; MARI: marking of the axillary lymph node with radioactive iodine seeds; BCS: breast conserving surgery

A   For 4% of patients, diagnosed in the Northwest region in 2008-2010, information on SLNB was not available.

B   Micrometastasis (>0.2-2mm) were included as positive result, whereas isolated tumor cell clusters (≤0.2mm) were not.

C   For 9% of patients who underwent surgery, mainly diagnosed in 2008-2010, information on resection margin status was not available. Focal residual tumors are tumors into the inked margin in an area of ≤4 mm.

D   Including the single cancer specific hospital in the Netherlands.

Radiotherapy use over time and according to age groups

An increasing percentage of patients received radiotherapy between 2008 (61%) and 2016 (70%), which is in line with the shift from mastectomy to BCT (Figure 1A). After 2016, radiotherapy use slightly decreased to 67% (2019), as the use of BCS without radiotherapy increased from 4% in 2016 to 9% in 2019. The number of women undergoing mastectomy decreased in 2008-2019, while the proportion receiving PMRT increased: 30% in 2008, 37% in 2015. Since 2015, this proportion remained constant. Women receiving PMRT more often had (y)pT2-4 (64%) and (y)pN+ (79%) disease and less often an R0-resection (94%) compared to those not receiving PMRT (41%, 27% and 99%, respectively). The percentage of women receiving no surgery (79% aged >75) remained stable over time (6-8%).

The shift from mastectomy to BCT, and hence increased radiotherapy use, was shown in all age groups (Figure 1B/C). Women aged 50-75, when compared to the other age groups, received BCS and radiotherapy most often. Patients aged <50 more frequently received mastectomy and less frequently BCS, hence they were less often irradiated than older patients. However, after a mastectomy, patients aged <50 received adjuvant radiotherapy more often than those aged ≥50. In patients aged >75, the proportion who underwent surgery decreased with increasing age. Mastectomy was applied more frequently than BCS in patients aged >75, and these older patients less often received radiotherapy following BCS than younger ones. This was most obvious in the period 2016-2019 (Figure 1C). Patients aged >75 who underwent no surgery more often received hormonal therapy (88%) than those who did undergo surgery (57%).

Older patients with smaller tumors also had surgery and subsequent radiotherapy omitted: patients aged >75 with cT1-2 cN0 disease underwent surgery slightly more often (72%) than all patients aged >75 (65%), and radiotherapy following BCS or mastectomy remained limited (Figure 1D).

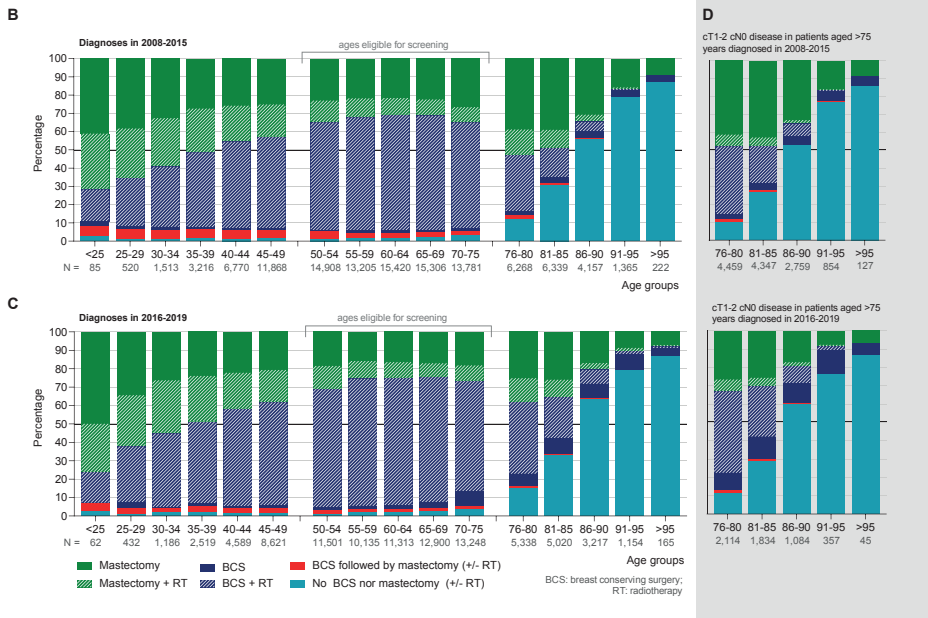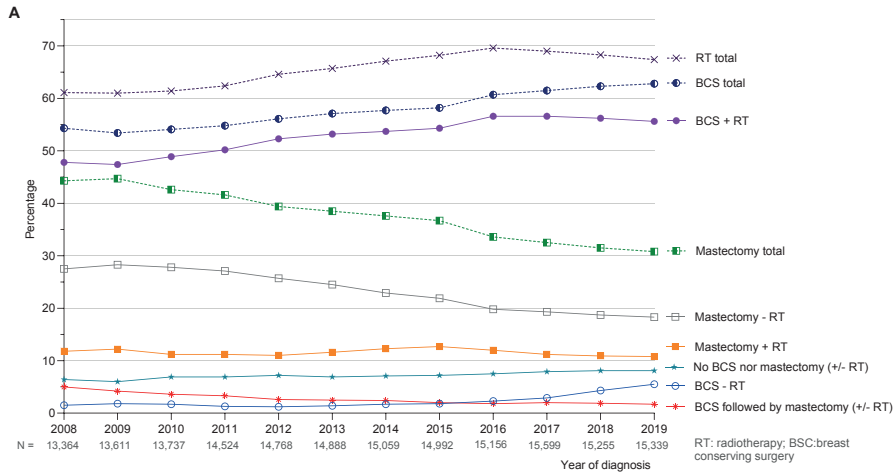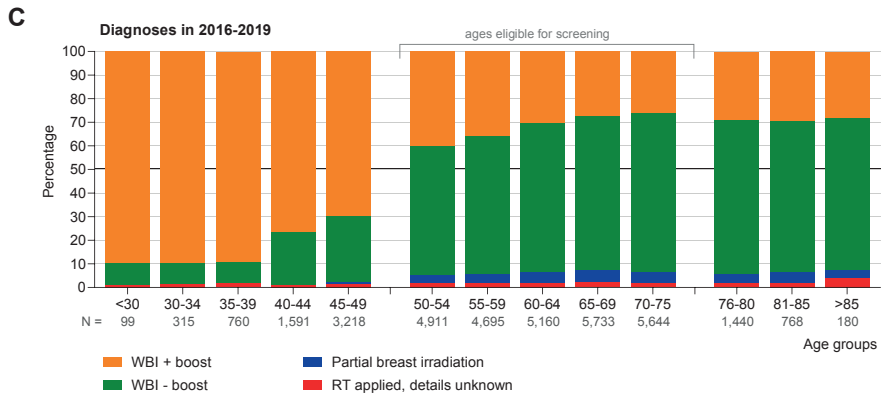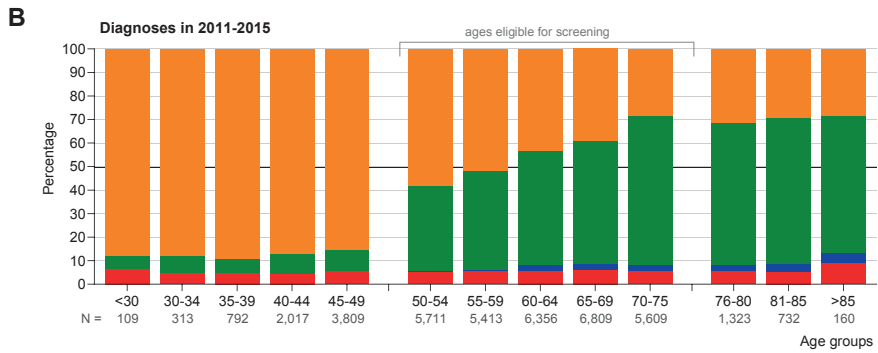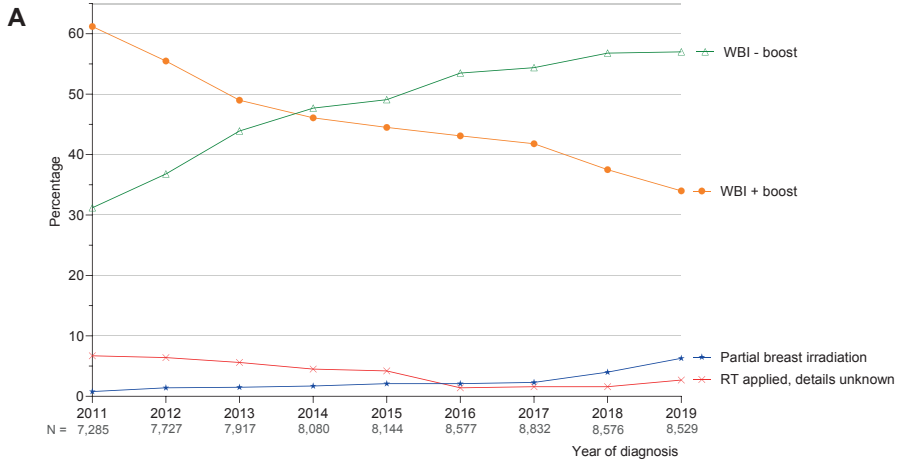**Figure 1.** Primary treatment in women diagnosed with invasive non-metastatic breast cancer in the Netherlands, [A] over the years of diagnosis, and according to age groups stratified for [B] 2008-2015, [C] 2016-2019 and [D] patients aged >75 with cT1-2 cN0 disease

PBI and boost irradiation

Radiotherapy following BCS increasingly concerned PBI: 1% (2011) to 6% (2019) (Figure 2A), which was mainly applied in women aged ≥50. Furthermore, BCT became increasingly administered without boost. In 2011, 66% of women who underwent BCS and WBI had a boost administered, compared to 37% in 2019. During 2011-2015, boost use decreased with increasing age starting from 50 years onwards (Figure 2B). In 2016-2019, this trend in decreased boost use started at 40 years (Figure 2C). In patients aged ≥70, no trend according to age groups nor time period was noted and ~30% received WBI with boost.

In women who underwent BCS, WBI with boost irradiation versus without was strongly associated with age (OR >75 vs <50:0.04, 95%CI:0.03-0.05), grade (OR grade III vs I:11.46, 95%CI:9.90-13.26), and resection margin status (OR focal residual tumor vs R0-resection:28.08, 95%CI:23.07-34.17). Also, patients diagnosed earlier in the study period and patients with lymph node metastases or higher T-stage, were more likely to receive a boost. The likelihood of receiving a boost varied among regions, but no associations were found for hospital characteristics (Table 2).

Figure 2. Radiotherapy administered in women diagnosed with invasive non-metastatic breast cancer in the Netherlands, who underwent BCS and no mastectomy and received radiotherapy, [A] over the years of diagnosis, and according to age groups stratified for [B] 2011-2015 and [C] 2016-2019

Table 2. Adjusted odds ratios (OR) of receiving whole breast irradiation (WBI) with boost versus without boost, after BCS [A], in women diagnosed with invasive non-metastatic breast cancer in the Netherlands

	WBI without boost		WBI with boost			
	N = 35,572		N = 33,480			
	n	(%)	n	(%)	OR [B]	(95%CI)
Median year of diagnosis (p25, p75)	2016	(2014-2018)	2015	(2012-2017)	**0.87** [C]	**(0.86-0.88)**
Age at time of diagnosis						
<50 years	1,942	(5.5)	10,626	(31.7)	Reference	
50-75 years	30,738	(86.4)	21,476	(64.1)	**0.09**	**(0.08-0.11)**
>75 years	2,892	(8.1)	1,378	(4.1)	**0.04**	**(0.03-0.05)**
Region of residence						
North	4,002	(11.3)	5,223	(15.6)	Reference	
East	6,072	(17.1)	5,546	(16.6)	**0.79**	**(0.69-0.91)**
South	9,802	(27.6)	6,242	(18.6)	**0.58**	**(0.49-0.68)**
Southwest	6,656	(18.7)	7,414	(22.1)	0.91	(0.77-1.08)
Northwest	9,040	(25.4)	9,055	(27.0)	0.93	(0.80-1.07)
Grade						
Grade I	12,283	(34.5)	5,981	(17.9)	Reference	
Grade II	18,425	(51.8)	12,404	(37.0)	**1.40**	**(1.21-1.60)**
Grade III	3,284	(9.2)	12,554	(37.5)	**11.46**	**(9.90-13.26)**
Unknown	1,580	(4.4)	2,541	(7.6)	**3.11**	**(2.64-3.66)**
Pathological T-stage						
(y)pT0	1,679	(4.7)	1,690	(5.0)	**0.42**	**(0.36-0.50)**
(y)pT1	28,356	(79.7)	23,415	(69.9)	Reference	
(y)pT2	5,129	(14.4)	7,693	(23.0)	**1.24**	**(1.08-1.44)**
(y)pT3	78	(0.2)	177	(0.5)	1.34	(0.92-1.96)
(y)pT4	31	(0.1)	47	(0.1)	**1.80**	**(1.03-3.15)**
(y)pTX	299	(0.8)	458	(1.4)	1.02	(0.80-1.30)
Pathological N-stage [D]						
(y)pN0	27,599	(77.6)	23,237	(69.4)	Reference	
(y)pN+	6,793	(19.1)	9,436	(28.2)	**1.46**	**(1.32-1.60)**
(y)pNX	1,180	(3.3)	807	(2.4)	**1.22**	**(1.04-1.42)**
Resection margin status [E]						
R0-resection	35,045	(99.0)	29,486	(88.7)	Reference	
R1-resection: focal residual tumor	273	(0.8)	3,536	(10.6)	**28.08**	**(23.07-34.17)**
R1-resection: more than focal residual tumor	72	(0.2)	232	(0.7)	**6.59**	**(4.62-9.41)**
Travel time to a radiotherapy facility						
<15 minutes	13,812	(38.8)	12,905	(38.5)	Reference	
15-30 minutes	19,082	(53.6)	17,596	(52.6)	0.94	(0.89-1.00)
>30 minutes	2,678	(7.5)	2,979	(8.9)	0.91	(0.83-1.01)

Continued

	WBI without boost		WBI with boost			
	N = 35,572		N = 33,480			
	n	(%)	n	(%)	OR [B]	(95%CI)
Hospital of diagnosis						
Non-university	33,695	(94.7)	31,630	(94.5)	Reference	
University [F]	1,877	(5.3)	1,850	(5.5)	0.97	(0.73-1.29)
Radiotherapy department in the hospital's organization						
No	29,763	(83.7)	27,472	(82.1)	Reference	
Yes	5,809	(16.3)	6,008	(17.9)	1.08	(0.92-1.27)
Volume of diagnoses in the hospital						
Low volume	4,842	(13.6)	5,140	(15.4)	Reference	
Intermediate volume	9,949	(28.0)	9,452	(28.2)	0.90	(0.77-1.06)
High volume	20,781	(58.4)	18,888	(56.4)	0.87	(0.74-1.01)

OR: odds ratio, WBI: whole breast irradiation, 95%CI: 95% confidence interval, p25: 25th percentile; p75: 75th percentile; T: tumor, N: lymph node; values in bold are statistically significant

A   984 irradiated women diagnosed in 2011-2019 underwent BCS and mastectomy and were excluded from these analyses.

B   Models with both a random intercept and random effect were applied for age, grade, T-stage, N-stage, resection margin status and travel time. The analysis on year of diagnosis was not adjusted, as none of the factors fulfilled the criteria for inclusion in the adjustment set. The analysis on age was adjusted for year of diagnosis, grade, T-stage and resection margin status. The analysis on region was adjusted for age. The analysis on grade was adjusted for age, year of diagnosis, T-stage and resection margin status. The analysis on T-stage was adjusted for age, year of diagnosis, grade, N-stage and resection margin status. The analysis on N-stage was adjusted for age, year of diagnosis, grade, T-stage and resection margin status. The analysis on resection margin status was adjusted for age, year of diagnosis, grade, T-stage and N-stage. The analysis on travel time was adjusted for year of diagnosis. The analysis on type of hospital was adjusted for volume of diagnoses and grade. The analyses on radiotherapy in the hospital and volume of diagnoses were adjusted for region. NB. The analysis on type of hospital was not adjusted for a radiotherapy department in the hospital, as this was considered a basic component of university hospitals.

C   Factor included as continuous variable, with value 2011 as reference value.

D   Micrometastasis (>0.2-2mm) were included as positive result, whereas isolated tumor cell clusters (≤0.2mm) were not.

E   Information on resection margin status was not available for 409 patients who underwent BCS and WBI. Focal residual tumors are tumors into the inked margin in an area of ≤4 mm..

F   Including the single cancer specific hospital in the Netherlands.

In about one tenth of the patients who received PMRT, a boost was administered, which remained stable over time (Supplementary Figure 2). Those who received boost irradiation in PMRT less often had an R0-resection (68%) compared to those who did not receive a boost (97%).

Regional radiotherapy

Regional radiotherapy was increasingly applied in patients with (y)pN+ and/or cN+ disease (32% in 2011, 61% in 2019), while use of ALND decreased from 76% to 24% (Figure 3A). ALND and regional radiotherapy were combined in 23% of patients in 2011 and 14% in 2019. Sixteen percent of women with (y)pN+ and/or cN+ disease received neither regional radiotherapy nor ALND in 2011, which increased to 29% in 2019. These patients possibly received WBI and/or systemic therapy, and frequently had cN0→(y)pN+ (57%, two thirds regarded lymph node micrometastases), cN+→(y)pNX (23%) or cN+→(y)pN0 disease (12%). In women with lymph node micrometastatic disease who underwent BCT, 52% received regional treatment, which was 46% in those who underwent mastectomy.

The shift from ALND to regional radiotherapy was shown in all age groups (Figure 3B/C). In 2011-2015, regional radiotherapy was administered in ~55% of patients aged ≤75 receiving regional treatment, which increased to ~80% in 2016-2019. In case of regional treatment in women aged >75 (54%), the proportion receiving regional radiotherapy was 47% in 2011-2015 and 68% in 2016-2019. Also, women aged >75 more frequently had regional radiotherapy combined with ALND than younger women, especially in 2016-2019.

Women with lymph node micrometastases were more likely to be treated with regional radiotherapy instead of ALND (OR:4.73, 95%CI:4.04-5.54) compared to women with macrometastases. More recent years of diagnosis were positively associated with regional radiotherapy, while higher T-stage and grade were negatively associated (Table 3), as well as higher performance status (Supplementary Table 2). Patients in the South (OR:0.65, 95%CI:0.45-0.96) and Southwest region (OR:0.55, 95%CI:0.37-0.80) were less likely to receive regional radiotherapy instead of ALND, compared to the North region. No associations were found for hospital characteristics.
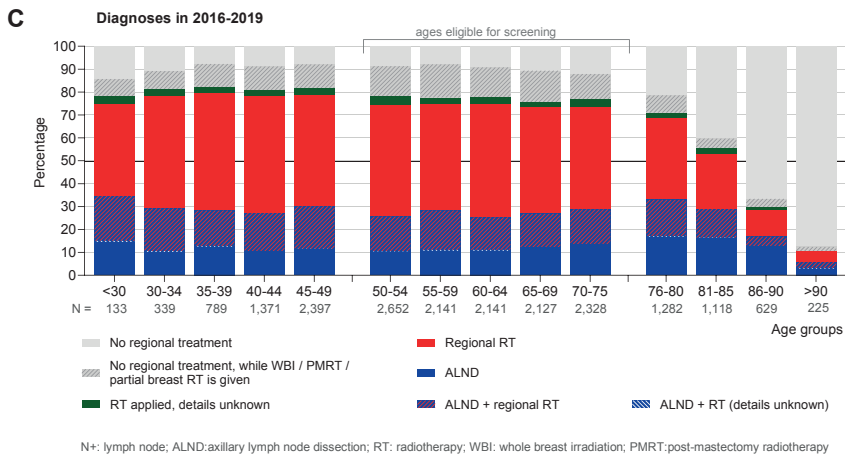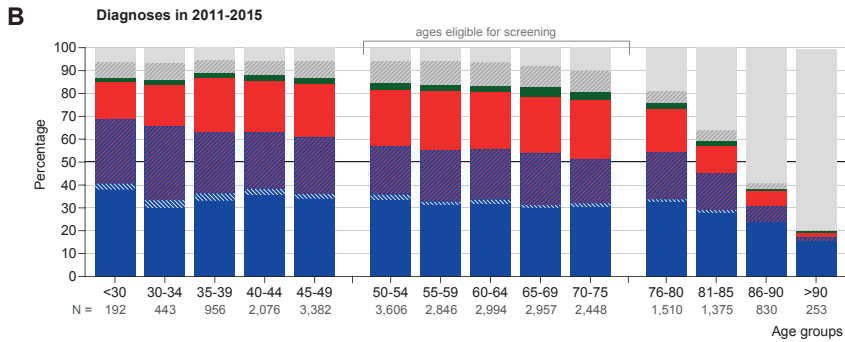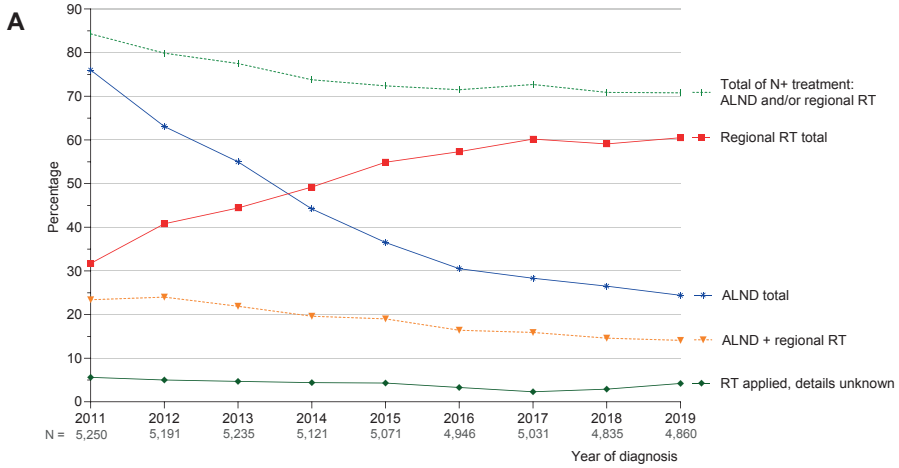
Figure 3. Regional treatment in women diagnosed with invasive non-metastatic (y) pN+ and/or cN+ breast cancer in the Netherlands, [A] over the years of diagnosis, and according to age groups stratified for [B] 2011-2015 and [C] 2016-2019

Table 3. Adjusted odds ratios (OR) of receiving regional radiotherapy versus axillary lymph node dissection (ALND) [A], in women diagnosed with invasive non-metastatic (y) pN+ and/or cN+ breast cancer in the Netherlands

	ALND		Regional radiotherapy			
	N = 11,076		N = 14,474			
	n	(%)	n	(%)	OR [B]	(95%CI)
Median year of diagnosis (p25, p75)	2013	(2012-2015)	2016	(2014-2018)	**1.62** [C]	**(1.60-1.65)**
Age at time of diagnosis						
<50 years	3,167	(28.6)	4,082	(28.2)	Reference	
50-75 years	6,274	(56.6)	9,089	(62.8)	**1.18**	**(1.06-1.32)**
>75 years	1,635	(14.8)	1,303	(9.0)	**0.68**	**(0.59-0.78)**
Region of residence						
North	1,607	(14.5)	1,941	(13.4)	Reference	
East	1,762	(15.9)	2,897	(20.0)	0.95	(0.71-1.29)
South	2,200	(19.9)	2,740	(18.9)	**0.65**	**(0.45-0.96)**
Southwest	3,401	(30.7)	2,295	(15.9)	**0.55**	**(0.37-0.80)**
Northwest	2,106	(19.0)	4,601	(31.8)	1.04	(0.76-1.42)
Grade						
Grade I	1,399	(12.6)	2,407	(16.6)	Reference	
Grade II	4,684	(42.3)	6,850	(47.3)	**0.84**	**(0.73-0.96)**
Grade III	3,653	(33.0)	3,830	(26.5)	**0.62**	**(0.53-0.71)**
Unknown	1,340	(12.1)	1,387	(9.6)	**0.78**	**(0.66-0.92)**
Pathological T-stage						
(y)pT0	4,444	(40.1)	7,411	(51.2)	Reference	
(y)pT1	4,749	(42.9)	4,573	(31.6)	**0.64**	**(0.55-0.74)**
(y)pT2	716	(6.5)	804	(5.6)	**0.63**	**(0.52-0.76)**
(y)pT3	214	(1.9)	113	(0.8)	**0.30**	**(0.22-0.42)**
(y)pT4	640	(5.8)	1,102	(7.6)	**0.70**	**(0.58-0.85)**
(y)pTX	313	(2.8)	471	(3.3)	**0.76**	**(0.60-0.96)**
Lymph node micrometastasis						
No, size >2mm	10,107	(91.3)	11,301	(78.1)	Reference	
Yes, size >0.2-2mm	969	(8.7)	3,173	(21.9)	**4.73**	**(4.04-5.54)**
Travel time to a radiotherapy facility						
<15 minutes	3,792	(34.2)	6,006	(41.5)	Reference	
15-30 minutes	6,067	(54.8)	7,492	(51.8)	0.98	(0.90-1.08)
>30 minutes	1,217	(11.0)	976	(6.7)	**0.83**	**(0.71-0.97)**
Hospital of diagnosis						
University [D]	10,324	(93.2)	13,566	(93.7)	Reference	
Non-university	752	(6.8)	908	(6.3)	1.04	(0.50-2.17)

Continued

	ALND		Regional radiotherapy			
	N = 11,076		N = 14,474			
	n	(%)	n	(%)	OR [B]	(95%CI)
Radiotherapy department in the hospital's organization						
No	9,107	(82.2)	11,539	(79.7)	Reference	
Yes	1,969	(17.8)	2,935	(20.3)	1.41	(0.63-3.18)
Volume of diagnoses in the hospital						
Low volume	1,826	(16.5)	2,035	(14.1)	Reference	
Intermediate volume	3,209	(29.0)	4,231	(29.2)	1.16	(0.63-2.14)
High volume	6,041	(54.5)	8,208	(56.7)	1.17	(0.64-2.15)

OR: odds ratio, ALND: axillary lymph node dissection, 95%CI: 95% confidence interval, p25: 25th percentile; p75: 75th percentile; T: tumor, values in bold are statistically significant

A   8,590 women diagnosed in 2011-2019 received both regional radiotherapy and ALND and were excluded from these analyses.

B   Models with both a random intercept and random effect were applied for age, grade, T-stage, lymph node micrometastasis and travel time. The analysis on year of diagnosis was not adjusted, as none of the factors fulfilled the criteria for inclusion in the adjustment set. The analysis on age was adjusted for year of diagnosis, grade, T-stage and lymph node micrometastasis. The analysis on region was adjusted for year of diagnosis, T-stage and travel time. The analysis on grade was adjusted for year of diagnosis, T-stage and lymph node micrometastasis. The analysis on T-stage was adjusted for age, year of diagnosis, grade and lymph node micr-metastasis. The analyses on lymph node micrometastasis and travel time were adjusted for year of diagnosis. The analysis on type of hospital was adjusted for year of diagnosis, region, travel time and volume of diagnoses. The analysis on radiotherapy in the hospital was adjusted for year of diagnosis, travel time and type of hospital. The analysis on volume of diagnoses was adjusted for year of diagnosis and travel time. NB. The analysis on type of hospital was not adjusted for a radiotherapy department in the hospital, as this was considered a basic component of university hospitals.

C   Factor included as continuous variable, with value 2011 as reference value.

D   Including the single cancer specific hospital in the Netherlands.

DISCUSSION

This nationwide study reports increased radiotherapy use as part of locoregional non-metastatic BC treatment from 2008 (61%) to 2016 (70%), caused by shifts from mastectomy to BCT, ALND to regional radiotherapy, and increased use of PMRT. In 2017-2019, radiotherapy use slightly decreased to 67%, as in older patients post-BCS radiotherapy was increasingly omitted. Further radiotherapy de-escalation was observed by decreased boost irradiation in BCT and increased PBI use.

Previously reported trends in the Netherlands

Increased radiotherapy use in non-metastatic BC treatment in the Netherlands was previously reported for 1997-2008 and 2011-2015, as both BCT and PMRT use increased[32,33]. We demonstrated discontinuations of these trends since 2016: the overall radiotherapy use slightly decreased, the use of BCS without radiotherapy increased, and radiotherapy in women undergoing mastectomy remained stable. Boost irradiation in BCT was previously reported to decrease in the Netherlands in 2011-2016[34] following treatment guideline revisions prescribing restrictive use of boost irradiation[4]. We showed a continuation of decreasing boost use in subsequent years.

Multiple trials showed no[14-17] or minimal inferiority[18] in terms of local recurrences for PBI instead of WBI following BCS in low-risk women. Subsequently, we showed that PBI use following BCS increased in the Netherlands, which was previously not quantified using nationwide data. PBI use also increased abroad[36-38], with even higher utilization rates observed in the US[38] – possibly resulting from the ASTRO-consensus statement on PBI being published already in 2009[39].

Post-BCS radiotherapy omission

Increased incidence of early BC[10] and improved prognosis[10,11] provided opportunity for personalized treatment and shared decision-making. This may have facilitated the observed increase of BCS without radiotherapy: long-term analyses show no survival benefit of adjuvant radiotherapy after BCS in elderly low-risk patients[20-22], who consequently may decline to receive radiotherapy after being informed on its advantages and disadvantages.

The Dutch TOP-1 trial (NTR6147) investigates the absolute local recurrence risk of omitting both radiotherapy and hormonal therapy after BCS in low-risk patients aged ≥70[19]. The observed increase of BCS without radiotherapy coincided with this trial's initiation. However, as the trial-accrual is lower than the observed increase of patients undergoing BCS without radiotherapy, our observations likely indicate an actual change in clinical practice. Radiotherapy following BCS was also increasingly omitted in the US, mainly in elderly patients[40]. In Germany, elderly patients likewise received radiotherapy following breast surgery less often (34%) than younger patients (79%)[41].

Post-BCT boost irradiation

Similar to our findings, boost irradiation in BCT decreased in the US in recent years[42]. Boost irradiation is associated with a reduced local recurrence rate at the cost of breast fibrosis and a worse cosmetic outcome[9,24,25]. Given the current low local recurrence rate, treatment guidelines nowadays suggest boost irradiation in BCT mainly in high-risk women[4,6,7,9,23,24]. We indeed showed that higher grade and T-stage, nodal involvement, and young age were associated with boost use in BCT. Decreasing boost use started from younger ages in 2016-2019 (40-44 years) compared to 2011-2015 (50-54 years). In an Australian and New-Zealand survey, radiation oncologists also indicated patients' age a key element in deciding to apply boost irradiation, although consensus lacked on age indications[43].

Women with focal residual tumor (≤4mm tumor area in the inked margin) had a high probability of receiving boost irradiation. In the Netherlands, boost irradiation in BCT is recommended alternatively to re-excision in patients with focal margin involvement[5], as re-excision in these patients is not associated with better disease-free and overall survival[44]. A Japanese survey also indicated resection margins to be a dominant factor in deciding on boost use[45]. Variation in boost irradiation in BCT was found by region, both in our study and in the US[42]. However, in our study, boost use did not vary for hospital characteristics or travel time for radiotherapy, whereas these factors could explain the variation in the US study[42]. Regional differences in the Netherlands likely resulted from differences in local treatment protocols.

Regional treatment

Multiple trials found comparable overall survival and locoregional recurrence rates for ALND and axillary radiotherapy without ALND in N+ disease[29-31]. The AMAROS trial, specifically targeting patients with cN0-pN1(sn) disease, found less morbidity without impeding locoregional control by axillary radiotherapy compared to ALND[29]. We observed increased regional radiotherapy and decreased ALND use in patients bearing (y)pN+ and/or cN+ disease, which are in line with these findings.

Studies also suggest that axillary treatment can be de-escalated after neoadjuvant systemic therapy in patients with cN+→(y)pN0 disease [46-48] or sentinel node micrometastases[49], which explains the observed omission of regional treatment in women with cN+→(y)pN0 and cN0→(y)pN-micrometastases.

Nevertheless, frequent regional treatment for micrometastases following WBI has been observed in our population, probably in consideration of lower radiation doses in the axilla with today's conformal WBI.

We found that women with more advanced disease were less likely to be treated with regional radiotherapy instead of ALND. However, 8,590 women received both regional radiotherapy and ALND, and were excluded from these analyses. These women were more frequently diagnosed with nodal macrometastases (98%), (y) pT2-4 (56%) and grade III tumors (34%) compared to women who received either regional radiotherapy or ALND. This suggests that the most advanced tumors were frequently treated with both regional radiotherapy and ALND.

The use of regional radiotherapy instead of ALND varied between region of residence and for patient characteristics as age. A US survey revealed a lack of uniform identification of patients eligible for axillary radiotherapy[50]. In the Netherlands, different local protocols hampered uniform decision on regional treatment. This, and possibly shared decision-making, may explain the observed variations for regional radiotherapy instead of ALND.

Strengths and limitations

Our study provides a nationwide and comprehensive overview of primary radiotherapy in the context of locoregional non-metastatic BC treatment for 12 recent years, using population-based data. We add to the existing knowledge by demonstrating continuations and discontinuations of previously reported trends, and by providing insight in both treatment variation and changed treatment patterns as a result of changing radiotherapy indications.

Limitations of our study include being unable to exclude boost irradiation on the axilla from tumor bed boost irradiation. Nevertheless, in BCT, regional boost irradiation is known to be limited compared to tumor bed boost irradiation (Supplementary Table 3). Furthermore, in regional radiotherapy, we could not define which axillary levels were treated. We did not have information on radiotherapy fractionation or dosage schedules. Hence, we could not evaluate the implementation of de-escalation by radiotherapy hypofractionation that is currently prescribed by treatment guidelines[4-7]. Also, data on the use of cardiac avoidance techniques were not available. Nevertheless, the Breath Hold technique is available everywhere in the Netherlands and standard practice in left-sided BC. As information on mutation status was not available, we could not investigate

to what extent this explains the higher frequency of mastectomy in younger women. Finally, the multivariable analyses could not be adjusted for comorbidities or performance status given their limited availability. In particular, the associations found for age will be affected by this residual confounding, hence partly reflect less intensive treatment because of performance rather than solely calendar age.

Conclusions

This nationwide study reports increased radiotherapy use in invasive non-metastatic BC treatment in 2008-2016, which results from treatment shifts from mastectomy to BCT and ALND to regional radiotherapy. Also, PMRT use increased in this period. Since 2016, radiotherapy de-escalation was observed as older patients more frequently received BCS without radiotherapy. Further radiotherapy de-escalation was seen by decreased boost irradiation in BCT and increasing PBI use. The observed de-escalation reflects recent changes in radiotherapy indications aiming to prevent treatment-related toxicity. In line with these changed indications, we observed that low-risk patients were most likely to have boost irradiation omitted. Both boost radiation and regional radiotherapy use varied across the country, which may reflect local treatment protocols and shared decision-making. Future treatment patterns will likely be impacted by recently published and currently ongoing studies (Supplementary Table 4) which aim to further de-escalate invasive BC treatment.

ACKNOWLEDGEMENTS

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Supplementary Figure 1. Classification of geographical regions in the Netherlands
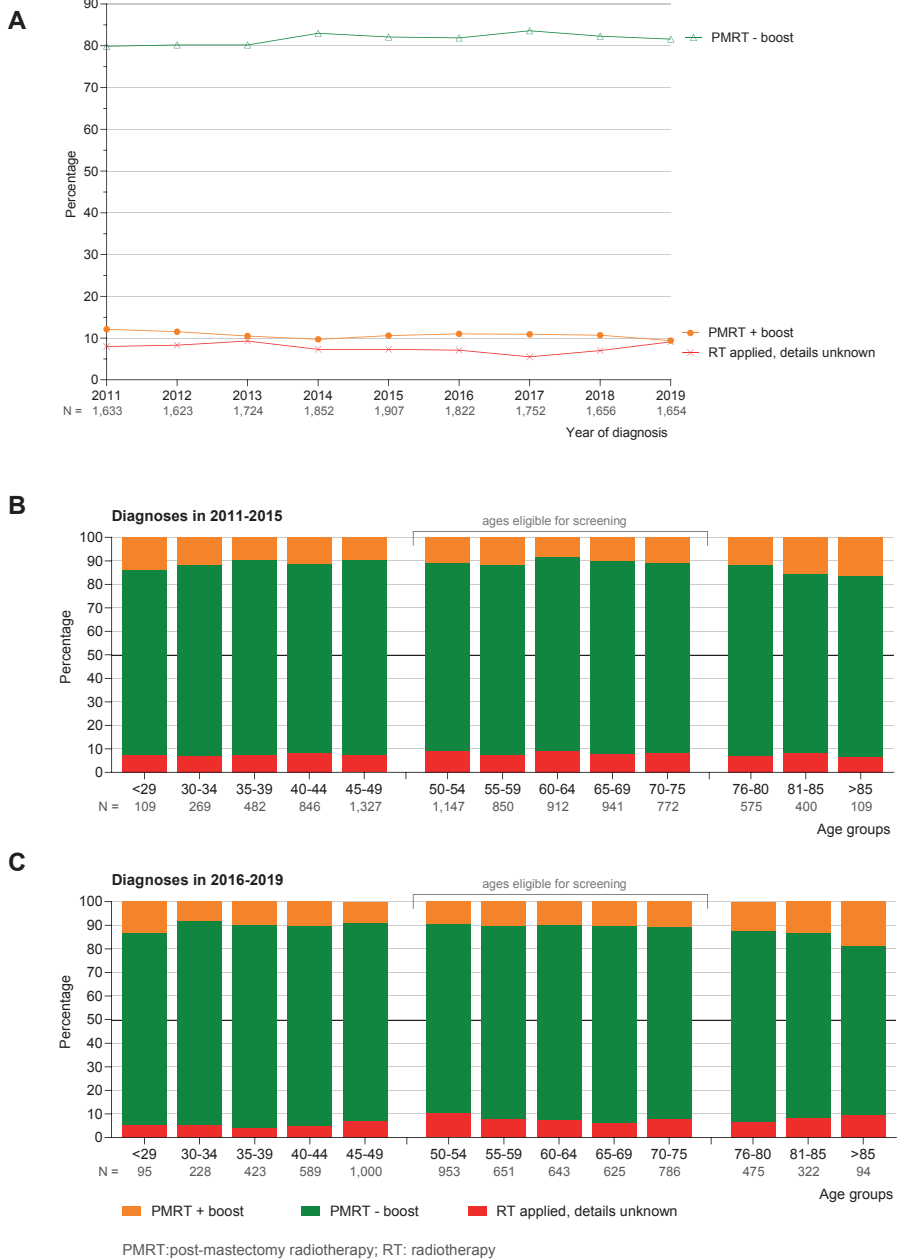
Supplementary Figure 2. Radiotherapy administered in women diagnosed with invasive non-metastatic breast cancer in the Netherlands, who underwent mastectomy and no BCS and received radiotherapy, [A] over the years of diagnosis, and according to age groups stratified for [B] 2011-2015 and [C] 2016-2019

Supplementary Table 1. Categorization of comorbidities

Categories used in the current study	Original Charlson Comorbidity Index categories
● Previous malignancy (M0/M+)	● Tumor without malignancy
	● Metastatic malignancy
	● Lymphoma
	● Leukemia
● Myocardial infarction	● Myocardial infarction
● Congestive heart failure	● Congestive heart failure
● Peripheral vascular disease	● Peripheral vascular disease
● Cerebrovascular disease / hemiplegia	● Cerebrovascular disease
	● Hemiplegia
● Chronic pulmonary disease	● Chronic pulmonary disease
● Diabetes Mellitus	● Diabetes Mellitus
	● Diabetes Mellitus with end organ damage
● Renal disease	● Moderate / severe renal disease
● Liver disease	● Mild liver disease
	● Moderate / severe liver disease
● Ulcer disease	● Ulcer disease
● Dementia	● Dementia
● Rheumatoid Arthritis	● Connective tissue disease
● HIV	● AIDS

Comorbidities which could not be included in the above categories were disregarded
Categories were not assigned weights

Supplementary Table 2. Information on limited available variables: [1] Comorbidities, performance status and MARI procedure in women diagnosed with invasive non-metastatic breast cancer, stratified for ages <50, 50-75 and >75 years. [2] Adjusted odds ratios (OR) of receiving WBI with boost versus without boost, after BCS[A], in women diagnosed with invasive non-metastatic breast cancer. [3] Adjusted OR of receiving regional radiotherapy versus ALND[B], in women diagnosed with invasive non-metastatic (y)pN+ and/or cN+ breast cancer

| | [1] | | | | | | [2] Adjusted OR of receiving WBI with boost versus without boost | | [3] Adjusted OR of receiving regional radiotherapy versus ALND | |
| | Aged <50 N = 35,540 | | Aged 50-75 N = 112,255 | | Aged >75 N = 28,497 | | | | | |
	n	(%)	n	(%)	n	(%)	OR[C]	(95%CI)	OR[D]	(95%CI)
Comorbidities assessed[E]	4,783	(13.5)	18,308	(16.3)	7,310	(25.7)				
No comorbidity in any CCI category	4,103	(85.8)	12,045	(65.8)	3,112	(42.6)	Reference		Reference	
Comorbidity in 1 CCI category	583	(12.2)	4,466	(24.4)	2,437	(33.3)	1.03	(0.88-1.20)	0.85	(0.60-1.19)
Comorbidities in >1 CCI category	97	(2.0)	1,797	(9.8)	1,761	(24.1)	**0.79**	**(0.63-0.98)**	0.76	(0.50-1.13)
Performance status available[F]	13,587	(38.2)	39,200	(34.9)	7,258	(25.5)				
Performance status 0	12,081	(88.9)	31,102	(79.3)	3,220	(44.4)	Reference		Reference	
Performance status 1	1,442	(10.6)	7,122	(18.2)	2,707	(37.3)	0.96	(0.86-1.06)	**0.71**	**(0.61-0.82)**
Performance status 2-4	64	(0.5)	976	(2.5)	1,331	(18.3)	0.81	(0.63-1.03)	**0.41**	**(0.31-0.54)**
MARI procedure performed[G]	1,661	(11.5)	2,271	(4.6)	143	(1.1)				

MARI: marking of the axillary lymph node with radioactive iodine seeds, OR: odds ratio, WBI: whole breast irradiation, BCS: breast-conserving surgery, ALND: axillary lymph node dissection, 95%CI: 95%-confidence interval, CCI: Charlson Comorbidity Index, values in bold are statistically significant

A   Women who underwent BCS and mastectomy were excluded from these analyses.

B   Women who received both regional radiotherapy and ALND were excluded from these analyses.

C   Models with both a random intercept and random effect were applied for both comorbidities and performance status. The analysis on comorbidities was adjusted for age, grade and resection margin status. The analysis on performance status was adjusted for age, year of diagnosis, grade, T-stage and resection margin status.

D   Models with both a random intercept and random effect were applied for both comorbidities and performance status. The analysis on comorbidities was adjusted for year of diagnosis and region. The analysis on performance status was adjusted for year of diagnosis and T-stage.

E   Never available for patients diagnosed outside the South region and neither for patients diagnosed in the South region since 2017.

F   Never available for patients diagnosed before 2011.

G   MARI-procedures were available since 2015.

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Supplementary Table 3. Boost irradiation in breast-conserving surgery (BCS) combined with whole breast irradiation (WBI)

69,052 women diagnosed in 2011-2019 underwent BCS and WBI	→	12,623 of these women received regional radiotherapy (18.3%)	→	7,387 of these women received boost irradiation (58.5%)	*This boost can be either tumor bed or regional boost irradiation*
			→	5,236 of these women received no boost irradiation (41.4%)	
(women receiving mastectomy following BCS were excluded)	→	56,429 of these women received no regional radiotherapy (81.7%)	→	26,093 of these women received boost irradiation (46.2%)	*This boost can only be tumor bed boost irradiation*
			→	30,336 of these women received no boost irradiation (53.8%)	

Supplementary Table 4. Recently published or currently ongoing studies which likely impact future treatment patterns of invasive non-metastatic breast cancer

Trial	ClinicalTrials.gov Identifier	Research topic
TOP-1	N/A	Various studies investigate if radiotherapy following breast conserving surgery can safely be omitted. The Dutch TOP-1 trial investigates omission of both radiotherapy and endocrine therapy in patients aged ≥70 with early-stage breast cancer. The LUMINA study and EXPERT trial target younger patients (aged ≥55 and ≥50, respectively) who receive endocrine therapy and bear low-risk luminal A breast cancer. The IDEA and PROSPECT studies and PRIME-II, PRECISION and PRIMETIME trials (aim to) identify low-risk women in whom radiotherapy can be omitted, using varying biomarker assays and cut-offs for age. In all of these studies, women are supposed to receive endocrine therapy. The NRG-BR007 DEBRA trial targets both women and men with low-risk tumor biology who receive endocrine therapy.
LUMINA	NCT01791829	
EXPERT	NCT02889874	
IDEA	NCT02400190	
PROSPECT	N/A	
PRIME-II	N/A	
PRECISION	NCT02653755	
PRIMETIME	N/A	
NRG-BR007 DEBRA	NCT04852887	
FASTs	N/A	Hypofractionation of whole breast irradiation following breast conserving surgery in early-stage breast cancer was investigated in the FAST and FAST-FORWARD trials. Both studies reported non-inferiority for hypofractionation; in the FAST trial in terms of normal tissue effects when comparing 28.5 Gy in 5 fractions compared to 50 Gy in 25 fractions, in the FAST-FORWARD trial in terms of local tumor control when comparing 26 Gy in 5 fractions compared to 40 Gy in 15 fractions.
FAST-FORWARD	NCT04148586	
SOUND	NCT02167490	Multiple trials investigate if sentinel lymph node biopsy in cN0 disease after ultrasound assessment is clinically beneficial or may be omitted. The SOUND, INSEMA, BOOG 2013-08, SOAPET and NAUTILUS trials target patients with early-stage breast cancer who undergo surgery. In the ASICS and EUBREAST-01 trials, specifically patients with favorable tumor biology are targeted.
INSEMA	NCT02466737	
BOOG 2013-08	NCT02271828	
SOAPET	NCT04072653	
NAUTILUS	NCT04303715	
ASICS	NCT04225858	
EUBREAST-01	NCT04101851	
ALLIANCE A11202	NCT01901094	The ALLIANCE A11202 trial investigates if radiotherapy to the regional lymph nodes and axilla without axillary lymph node dissection is inferior to radiotherapy to the regional lymph nodes with axillary lymph node dissection, in patients with positive sentinel lymph nodes after neoadjuvant chemotherapy and breast surgery.
NSABP-51 / NRG9353	NCT01872975	The added value of regional radiotherapy in addition to chest wall radiation following mastectomy or whole breast irradiation following breast-conserving surgery in patients with ypN0 disease after neoadjuvant therapy and breast surgery is investigated in the NSABP-51 / NRG9353 trial.

5

CHAPTER

6

Brachymonotherapy
in low-risk prostate cancer

TRENDS AND VARIATION IN THE USE OF RADIOTHERAPY IN NON-METASTATIC PROSTATE CANCER: A 12-YEAR NATIONWIDE OVERVIEW FROM THE NETHERLANDS

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ABSTRACT

Purpose:

This population-based study describes nationwide trends and variation in the use of primary radiotherapy for non-metastatic prostate cancer in The Netherlands in 2008-2019.

Methods:

Prostate cancer patients were selected from the Netherlands Cancer Registry (N=103,059). Treatment trends were studied over time by prognostic risk groups. Multilevel analyses were applied to identify variables associated with external beam radiotherapy (EBRT) and brachy-monotherapy versus no active treatment in low-risk disease, and EBRT versus radical prostatectomy in intermediate and high-risk disease.

Results:

EBRT use remained stable (5-6%) in low-risk prostate cancer and increased from 21% to 32% in intermediate-risk, 37% to 45% in high-risk localized and 50% to 57% in high-risk locally advanced disease. Brachy-monotherapy decreased from 19% to 6% and from 15% to 10% in low and intermediate-risk disease, respectively, coinciding an increase of no active treatment from 55% to 73% in low-risk disease. Use of EBRT or brachy-monotherapy versus no active treatment in low-risk disease differed by region, T-stage and patient characteristics. Hospital characteristics were not associated with treatment in low-risk disease, except for availability of brachy-monotherapy in 2008-2013. Age, number of comorbidities, travel time for EBRT, prognostic risk group, and hospital characteristics were associated with EBRT versus prostatectomy in intermediate and high-risk disease.

Conclusion:

Intermediate/high-risk PCa was increasingly managed with EBRT, while brachy-monotherapy in low/intermediate-risk PCa decreased. In low-risk PCa, the no active treatment-approach increased. Variation in treatment suggests treatment decision related to patient/disease characteristics. In intermediate/high-risk disease, variation seems furthermore related to the treatment modalities available in the diagnosing hospitals

INTRODUCTION

Prostate cancer (PCa) is one of the most frequently diagnosed types of cancer among men in Western countries [1]. In recent years, approximately 12,500 men in The Netherlands were diagnosed with PCa annually, ~75% of whom with non-metastatic disease [2]. Non-metastatic PCa includes both localized and locally advanced disease and is classified in prognostic risk groups, which in The Netherlands are generally based on the European Association of Urology (EAU) classification [3].

Radiotherapy is a treatment option in all risk groups. In low-risk PCa, however, deferred treatment with active surveillance has been preferred since ~2009/2010 in selected patients and thereafter in all patients with low-risk PCa [3-5], as the harm of immediate treatment outweighs the benefits [6]. Also in intermediate-risk PCa active surveillance can be considered, but only for patients with favorable tumor characteristics [3-5]. In most patients with intermediate-risk PCa, external beam radiotherapy (EBRT) – with or without hormonal androgen deprivation therapy (ADT) and/or brachytherapy-boost is a recommended curative-intent treatment strategy, as are brachy-monotherapy and radical prostatectomy (RP) [3-5]. In high-risk PCa, EBRT combined with long term ADT and optionally a brachytherapy-boost, as well as RP followed by salvage EBRT in case of residual disease, are recommended [3-5]. Since high-quality evidence concluding superiority of either radiotherapy or RP is lacking, patients' preferences and tumor characteristics should drive the choice in treatment in intermediate and high-risk disease [7,8]. Watchful waiting can be considered in any risk group when life expectancy is limited or definitive treatment is not feasible [3-5].

Within Western countries considerable variation in radiotherapy use in non-metastatic PCa has been observed [9-13]. This suggests that the choice of treatment is based on local protocols, physician and/or patient preferences, and the availability of treatment modalities. In recent decades, the availability of radiotherapy and RP has changed in The Netherlands. Since 2008, thirteen additional EBRT facilities have opened, resulting in eighteen institutes performing EBRT in thirty-three facilities, and the number of facilities performing brachytherapy declined. Also hypofractionated EBRT was implemented for low and intermediate-risk PCa. Moreover, robot-assisted RP became widely

available and a minimum volume norm for RP has been introduced (>20 annually since 2012, >50 since 2018 and ≥100 since 2019). These developments and the implemented recommendation of active surveillance in low-risk disease, may have changed the previously reported use of radiotherapy for PCa in The Netherlands [9,14-16].

No nationwide overview of trends and variation in the use of radiotherapy as part of non-metastatic PCa treatment is available for the period since 2008. This nationwide study aims to investigate trends and variation in the use of radiotherapy versus other treatment approaches in low-risk, intermediate-risk, and high-risk localized PCa as well as locally advanced PCa in 2008-2019 in The Netherlands.

MATERIALS AND METHODS

Patients

Patients diagnosed with localized (cT1-2 cN0) or locally advanced (cT3-4 cN0/cT1-4 cN1) PCa in 2008-2019, who could be assigned an EAU prognostic risk group (section 2.2), were selected from the Netherlands Cancer Registry (NCR). The population-based NCR contains information on patients, disease, and primary treatment of all patients diagnosed with cancer in The Netherlands. These data were extracted from Dutch hospitals' medical records by trained registrars. Pathologically and clinically diagnosed patients were included. Patients living, diagnosed, or treated abroad, or diagnosed during autopsy or cystoprostatectomy were excluded.

Definitions

Clinical T-stage (cT) was based on TNM6 (2008-2009), TNM7 (2010-2016) and TNM8 (2017-2019). Prostate specific antigen values (PSA) at time of diagnosis were available. Gleason scores (GS) were based on biopsy specimens, except for patients diagnosed before 2013 who underwent an RP. For them GS were based on the RP specimen.

The EAU classification for prognostic risk groups was applied [3]. However, to reflect the risk stratification frequently applied in Dutch clinical practice, we considered cT2c-tumors with only low or intermediate-risk features as intermediate-risk. Low-risk disease was consequently defined as cT1-2a-tumors

with GS<7 and PSA<10 ng/ml; intermediate-risk disease as cT2b-c-tumors or GS7 or PSA10-20 ng/ml; and high-risk disease as GS>7 or PSA>20 ng/ml or locally advanced disease (cT3-4 cN0/cT1-4 cN1).

EBRT was defined as EBRT +/- hormonal therapy +/- brachytherapy-boost. Brachy-monotherapy was defined as brachytherapy +/- hormonal therapy but without EBRT or RP. RP was defined as prostatectomy +/- radiotherapy +/- hormonal therapy. No active treatment included both active surveillance and watchful waiting.

To assess variation across the country, we divided The Netherlands into five geographical regions based on patients' residence, each including ≥11 hospitals of which ≥1 university hospital and ≥3 radiotherapy institutes. We calculated patients' travel time for a one-way car trip to the nearest EBRT facility, using the postal codes of radiotherapy facilities and patient residency and the 2013-GEODAN drive time matrix [17].

For each patient, we classified whether the diagnosing hospital at time of diagnosis 1) was a university medical center, 2) had a radiotherapy department in its organization (not including other institute's departments in the same building), 3) had brachytherapy facilities available in its radiotherapy department, and 4) performed RPs. Also, the hospital's number of low-risk and intermediate/high-risk PCa diagnoses in 2008-2013 and 2014-2019 were determined and used to categorize half of the hospitals as low and half as high-volume.

Comorbidities at the time of diagnoses were registered for patients diagnosed before 2015 in the South of The Netherlands (~15%) and at national level for patients diagnosed in October 2015-March 2016 [16].

Analyses

Patient and disease characteristics, as well as trends and frequencies of primary treatment over time and by five-year age groups, were described stratified for low, intermediate, and high-risk localized and locally advanced disease. Distribution of treatment by age groups were further stratified for 2008-2013 and 2014-2019, allowing for comparison of treatment distributions in the older and most recent years. Only results for age groups with ≥50 patients were presented.

Variations in treatment were assessed by identifying associations of patient, tumor, and hospital-related variables with treatment in multilevel adjusted

analyses. In low-risk PCa, associations with 1) EBRT versus no active treatment and 2) brachy-monotherapy versus no active treatment were assessed. In intermediate and high-risk PCa, associations with EBRT versus RP were assessed. As treatment options were largely similar, intermediate and high-risk PCa, including locally advanced disease, were combined in these analyses.

Distinct models were created for each association investigated, stratified for 2008-2013 and 2014-2019 to allow for comparing the older and most recent years. A model included a random effect and random intercept for the various hospitals if the AICc-fit statistic improved, compared to the model with only a random intercept. This multilevel approach corrected for nesting of patients in hospitals. In addition, sets of variables for adjustment were selected for each investigated association separately (see footnotes of the applicable Tables). Variables were included when univariable inclusion resulted in at least 5% change in the odds ratio (OR) of interest compared to the unadjusted multilevel OR. Ninety-five percent confidence intervals (95%CI) were calculated and reflect probable OR-estimates, using a p-value (two-sided) of 0.05 as critical level for statistically significance. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 131,910 men were diagnosed with PCa in 2008-2019. This study includes 103,059 men with non-metastatic PCa; 22%, 37%, and 17% with low, intermediate, and high-risk localized PCa, respectively, and 24% with locally advanced PCa. Patients with low-risk PCa were younger (median: 66 years) compared to those with intermediate-risk (68 years), high-risk localized (72 years) and locally advanced disease (71 years). Distribution of region and hospital characteristics were largely similar across the risk groups (Table 1).

In low-risk disease, EBRT remained stable over time (5-6%) and was most frequently applied in men aged 70-79 years (Figure 1). Brachy-monotherapy and RP decreased from 19% (2008) to 6% (2019) and from 19% to 15%, respectively, while management with no active treatment increased from 55% to 73%. With increasing age, more patients received no active treatment whereas less received brachy-monotherapy or RP.

Table 1. Characteristics of patients diagnosed with prostate cancer in 2008-2019 in The Netherlands, stratified for low, intermediate and high-risk localized and locally advanced prostate cancer

	Localized						Locally advanced	
	Low-risk		Intermediate-risk		High-risk			
	N = 22,784		N = 37,767		N = 17,777		N = 24,731	
	n	(%)	n	(%)	n	(%)	n	(%)
Year of diagnosis								
2008-2010	5,208	(22.9)	8,852	(23.4)	4,890	(27.5)	5,081	(20.5)
2011-2013	6,016	(26.4)	10,038	(26.6)	4,663	(26.2)	6,174	(25.0)
2014-2016	5,733	(25.2)	8,452	(22.4)	3,796	(21.4)	6,670	(27.0)
2017-2019	5,827	(25.6)	10,425	(27.6)	4,428	(24.9)	6,806	(27.5)
Age at time of diagnosis, years								
<65	9,409	(41.3)	11,344	(30.0)	3,469	(19.5)	5,260	(21.3)
65 - <75	11,053	(48.5)	18,988	(50.3)	7,561	(42.5)	11,262	(45.5)
≥75	2,322	(10.2)	7,435	(19.7)	6,747	(38.0)	8,209	(33.2)
Median age at diagnosis (p25, p75)	66.0	(61.0-71.0)	68.0	(63.0-73.0)	72.0	(66.0-78.0)	71.0	(66.0-76.0)
Geographical region								
North	2,937	(12.9)	5,030	(13.3)	2,550	(14.3)	2,670	(10.8)
East	3,374	(14.8)	5,980	(15.8)	2,719	(15.3)	4,765	(19.3)
South	5,755	(25.3)	8,765	(23.2)	3,864	(21.7)	5,637	(22.8)
South West	5,245	(23.0)	8,296	(22.0)	4,207	(23.7)	5,197	(21.0)
North West	5,473	(24.0)	9,696	(25.7)	4,437	(25.0)	6,462	(26.1)
Hospital of diagnosis								
University hospital [A]	1,362	(6.0)	2,801	(7.4)	1,108	(6.2)	1,749	(7.1)
Radiotherapy department embedded	3,993	(17.5)	7,194	(19.1)	3,109	(17.5)	5,000	(20.2)
Performed brachytherapy	2,657	(11.7)	4,782	(12.7)	1,930	(10.9)	3,361	(13.6)
Performed prostatectomies	14,463	(63.5)	23,740	(62.9)	11,111	(62.5)	15,322	(62.0)

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Continued

	Localized						Locally advanced	
	Low-risk		Intermediate-risk		High-risk			
	N = 22,784		N = 37,767		N = 17,777		N = 24,731	
	n	(%)	n	(%)	n	(%)	n	(%)
Comorbidities at diagnosis being assessed [B]	3,908	(17.2)	5,734	(15.2)	2,749	(15.5)	4,042	(16.3)
At least 1 comorbidity present	2,318	(59.3)	3,701	(64.5)	1,996	(72.6)	2,891	(71.5)
Median number of comorbidities (p25,p75)	1.0	(0.0-1.0)	1.0	(0.0-2.0)	1.0	(0.0-2.0)	1.0	(0.0-2.0)
Most frequent comorbidities								
Hypertension	1,209	(30.9)	1,938	(33.8)	983	(35.8)	1,440	(35.6)
Diabetes Mellitus	388	(9.9)	694	(12.1)	453	(16.5)	621	(15.4)
Myocardial Infarction	344	(8.8)	581	(10.1)	375	(13.6)	570	(14.1)

p25: 25th percentile, p75: 75th percentile

A   Including the single cancer specific hospital in The Netherlands.

B   Comorbidities were available for patients diagnosed in the South before 2015 and for all patients diagnosed in Q4 2015-Q1 2016.
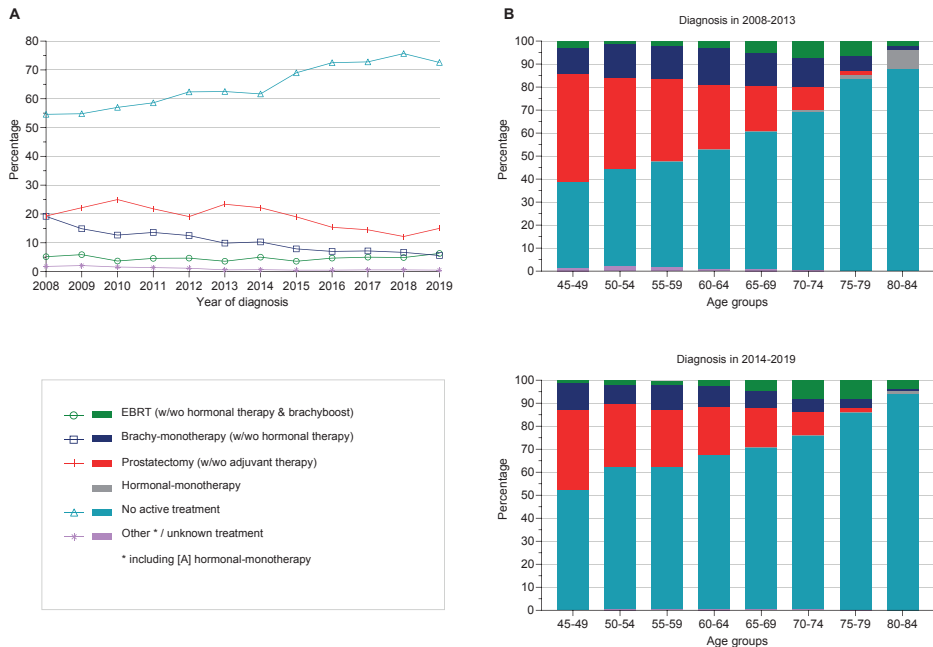
Figure 1. Primary treatment in patients diagnosed with low-risk localized prostate cancer in The Netherlands [A] over the years of diagnosis, N = 22,784, and [B] according to 5-year age groups stratified for 2008-2013, N = 11,154, and 2014-2019, N = 11,525

In multilevel analyses in low-risk PCa, higher cT, higher age and more comorbidities were positively associated with EBRT versus no active treatment in both 2008-2013 and 2014-2019 (Table 2). Living in the North of The Netherlands was associated with a higher probability of EBRT. Only in 2008-2013, year of diagnosis was associated with EBRT versus no active treatment; over time patients were less likely to receive EBRT. For all other variables no clear associations with EBRT were found.

Brachy-monotherapy use in low-risk PCa decreased by year in multilevel analyses (Table 2). Lower age and higher cT were positively associated with brachytherapy versus no active treatment in both 2008-2013 and 2014-2019. Patients in the South compared to the North were more likely to receive brachytherapy in 2014-2019. Only in the period 2008-2013, being diagnosed in a hospital that performed brachytherapy was associated with a higher probability of receiving brachytherapy instead of no active treatment. No clear associations with brachytherapy were found for other variables.

Table 2. Adjusted odds ratios (OR) of receiving EBRT versus no active treatment and brachytherapy versus no active treatment in patients with low-risk localized prostate cancer in The Netherlands, stratified for diagnoses in 2008-2013 and 2014-2019

	OR for receiving EBRT versus no active treatment			
	2008-2013 EBRT N = 516, No active treatment N = 6570		2014-2019 EBRT N = 568, No active treatment N = 8196	
	OR [A]	(95%CI)	OR [A]	(95%CI)
Year of diagnosis (continuously)	**0.90**	**(0.85-0.95)**	1.05	(1.00-1.11)
Age at time of diagnosis, years				
< 65	Reference		Reference	
65 - <75	**1.67**	**(1.35-2.07)**	**2.29**	**(1.82-2.87)**
≥75	1.06	(0.77-1.46)	**2.14**	**(1.59-2.87)**
Number of comorbidities at diagnosis [B]				
0	Reference		Reference	
1	**1.87**	**(1.06-3.30)**	**4.34**	**(2.06-9.15)**
≥2	1.66	(0.89-3.10)	**5.37**	**(2.55-11.28)**
Geographical region				
North	Reference		Reference	
East	**0.49**	**(0.30-0.80)**	**0.47**	**(0.30-0.74)**
South	**0.55**	**(0.35-0.86)**	**0.51**	**(0.33-0.79)**
South West	0.70	(0.45-1.08)	**0.62**	**(0.41-0.94)**
North West	**0.48**	**(0.31-0.74)**	**0.48**	**(0.32-0.71)**
Travel time (car) for EBRT, minutes				
<15	Reference		Reference	
15-30	1.09	(0.82-1.44)	1.21	(0.98-1.49)
>30	1.41	(0.96-2.06)	1.09	(0.74-1.60)
Clinical T-stage				
T1	Reference		Reference	
T2a	**2.54**	**(2.01-3.23)**	**2.14**	**(1.73-2.65)**
Type of hospital				
University [C]	Reference		Reference	
Non-university	1.31	(0.76-2.28)	1.38	(0.78-2.42)
Radiotherapy department in the hospital				
No	Reference		Reference	
Yes	0.70	(0.47-1.05)	1.11	(0.68-1.82)
Volume of low-risk PCa diagnoses in the hospital [D]				
Low volume	Reference		Reference	
High volume	0.89	(0.65-1.21)	1.11	(0.80-1.55)

Continued

OR for receiving brachytherapy versus no active treatment				
	2008-2013 Brachytherapy N = 1531, No active treatment N = 6570		2014-2019 Brachytherapy N = 852, No active treatment N = 8196	
	OR [E]	(95%CI)	OR [E]	(95%CI)
Year of diagnosis (continuously)	**0.88**	**(0.85-0.91)**	**0.87**	**(0.83-0.91)**
Age at time of diagnosis, years				
< 65	Reference		Reference	
65 - <75	**0.63**	**(0.56-0.71)**	**0.60**	**(0.50-0.72)**
≥75	**0.16**	**(0.12-0.22)**	**0.26**	**(0.18-0.37)**
Number of comorbidities at diagnosis [B]				
0	Reference		Reference	
1	0.82	(0.60-1.13)	0.83	(0.55-1.26)
≥2	0.80	(0.56-1.15)	1.01	(0.66-1.55)
Geographical region				
North	Reference		Reference	
East	1.30	(0.78-2.17)	1.53	(0.93-2.53)
South	1.09	(0.64-1.89)	**1.86**	**(1.12-3.09)**
South West	1.00	(0.58-1.70)	1.46	(0.88-2.41)
North West	0.90	(0.54-1.49)	1.17	(0.71-1.91)
Clinical T-stage				
T1	Reference		Reference	
T2a	**2.04**	**(1.69-2.45)**	**2.12**	**(1.75-2.57)**
Type of hospital				
University [C]	Reference		Reference	
Non-university	1.45	(0.71-2.94)	1.22	(0.62-2.41)
Brachytherapy is performed in the hospital				
No	Reference		Reference	
Yes	**1.75**	**(1.03-2.98)**	1.35	(0.03-52.75)
Volume of low-risk PCa diagnoses in the hospital [D]				
Low volume	Reference		Reference	
High volume	1.27	(0.87-1.84)	1.11	(0.78-1.57)

OR: odds ratio, EBRT: external beam radiotherapy, 95%CI: 95% confidence interval, PCa: prostate cancer; values in bold are statistically significant

Continued

A Models with both a random intercept and random effect were applied for the analyses on travel time for EBRT (2008-2013) and clinical T-stage. The analyses on year of diagnosis, travel time for EBRT (2014-2019), clinical T-stage, and volume of diagnoses in the hospital were not adjusted, as none of the variables fulfilled the criteria for inclusion in the adjustment set. The analysis on number of comorbidities (2008-2013) was adjusted for clinical T-stage and age. The analysis on number of comorbidities (2014-2019) was adjusted for age. The analyses on age, region, travel time for EBRT (2008-2013), type of hospital (2014-2019), and radiotherapy department in the hospital (2008-2013) were adjusted for clinical T-stage. The analysis on type of hospital (2014-2019) was adjusted for clinical T-stage and region. The analysis on radiotherapy department in the hospital (2014-2019) was adjusted for type of hospital and travel time for EBRT. Comorbidities were not included in adjustment sets considering their limited availability. The analysis on type of hospital was not adjusted for a radiotherapy department in the hospital, as this was considered a basic component of university hospitals.

B Comorbidities were available for patients diagnosed in the South before 2015 and for all patients diagnosed in October 2015-March 2016.

C Including the single cancer specific hospital in The Netherlands.

D Patients diagnosed in the 50% of hospitals with the lowest annual average number of low-risk prostate cancer diagnoses: <21 patients, were categorized in low volume. The remaining patients in the high volume-category.

E Models with both a random intercept and random effect were applied for the analyses on age (2014-2019), clinical T-stage and brachytherapy performed in the hospital (2014-2019). The analyses on year of diagnosis, and volume of diagnoses in the hospital were not adjusted, as none of the variables fulfilled the criteria for inclusion in the adjustment set. The analyses on number of comorbidities, and clinical T-stage were adjusted for age. The analyses on age (2008-2013), and region (2014-2019) were adjusted for clinical T-stage. The analysis on age (2014-2019) was adjusted for year of diagnosis and clinical T-stage. The analysis on region (2008-2013) was adjusted for age and brachytherapy performed in the hospital. The analysis on type of hospital (2008-2013) was adjusted for year of diagnosis, age, brachytherapy performed in the hospital and volume of diagnoses in the hospital. The analysis on type of hospital (2014-2019) was adjusted for clinical T-stage, age, brachytherapy performed in the hospital and volume of diagnoses in the hospital. The analysis on brachytherapy performed in the hospital was adjusted for type of hospital. Comorbidities were not included in adjustment sets considering their limited availability.

In intermediate-risk disease, EBRT increased from 21% (2008) to 32% (2019) (Figure 2). This increase occurred mainly in men aged 75-84 years. Brachy-monotherapy use decreased from 15% to 10%, while the application of RP varied between 33-41%. A quarter of patients – mainly elderly – received no active treatment; this proportion remained stable over time.

Figure 2. Primary treatment in patients diagnosed with intermediate-risk localized prostate cancer in The Netherlands [A] over the years of diagnosis, N = 37,767, and [B] according to 5-year age groups stratified for 2008-2013, N = 18,861, and 2014-2019, N = 18,847

In high-risk localized disease, EBRT and RP increased from 37% (2008) to 45% (2019) and 24% to 34%, respectively (Figure 3.1). Adjuvant EBRT was applied in 6% of RPs. EBRT use mainly increased in men aged 75-84 years, while younger men more frequently underwent RP. Hormonal-monotherapy decreased from 21% to 7%. One sixth of patients received no active treatment, which remained stable over time. Most patients receiving hormonal-monotherapy or no active treatment were elderly.

In locally advanced disease, EBRT and RP increased from 50% (2008) to 57% (2019) and 7% to 15%, respectively (Figure 3.2). Seven percent of RPs were followed by EBRT. EBRT use mainly increased in men aged 75-84 years. Over time, less patients received hormonal-monotherapy (36% versus 18%) and application of no active treatment slightly increased (7-10%). Hormonal-monotherapy and no active treatment were given mainly in elderly patients.
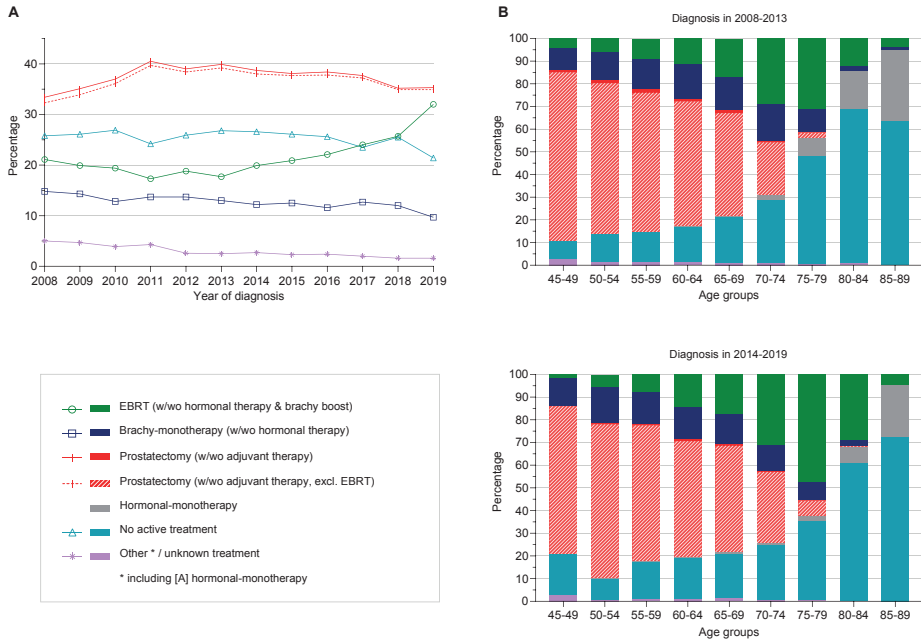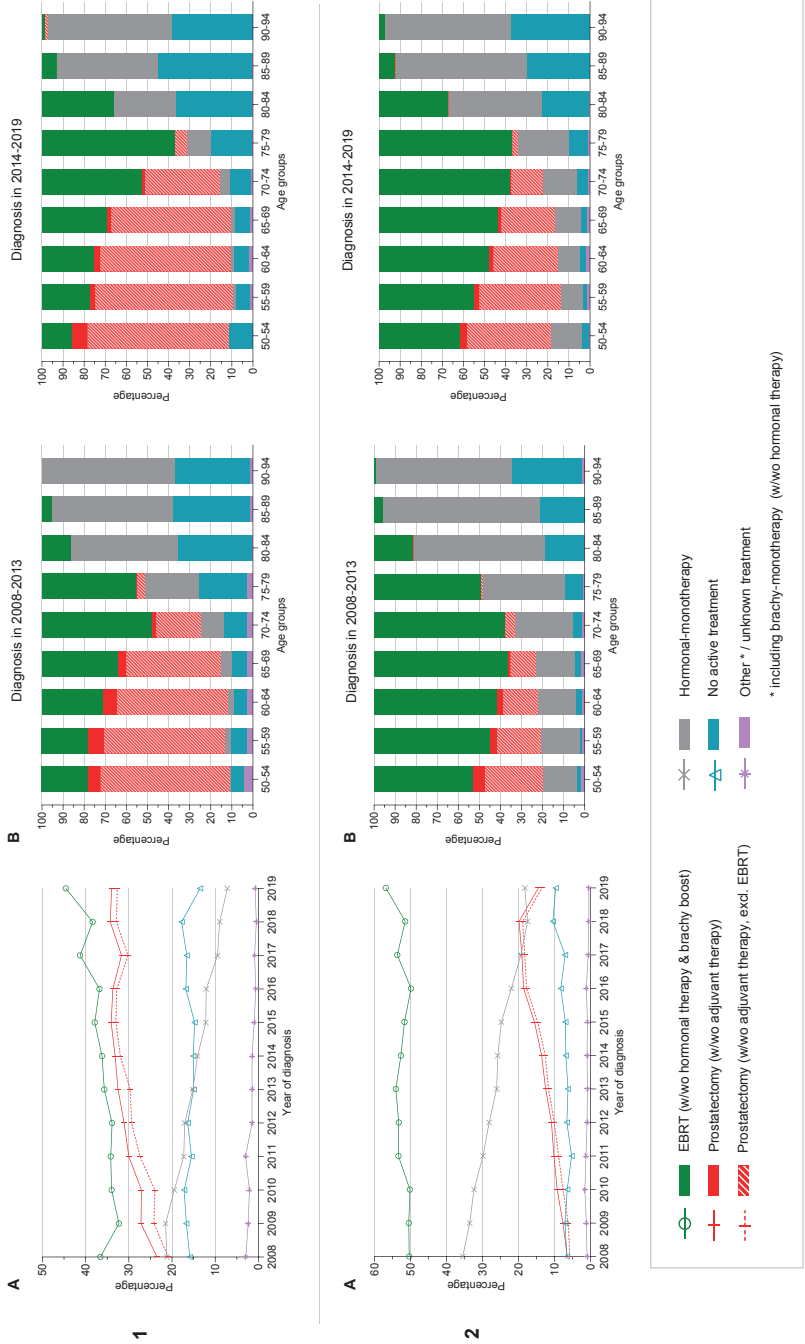
Figure 3. Primary treatment in patients diagnosed with [1] high-risk localized prostate cancer in The Netherlands [A] over the years of diagnosis, N = 17,777, and [B] according to 5-year age groups stratified for 2008-2013, N = 9,496, and 2014-2019, N = 8,193, and [2] locally advanced prostate cancer in The Netherlands [A] over the years of diagnosis, N = 24,731, and [B] according to 5-year age groups stratified for 2008-2013, N = 11,198, and 2014-2019, N = 13,408

In multilevel analyses in patients with intermediate or high-risk PCa, use of EBRT versus RP decreased by year of diagnosis in 2008-2013 and increased in 2014-2019 (Table 3). Higher age, more comorbidities and less travel time for EBRT were positively associated with EBRT versus RP in both 2008-2013 and 2014-2019. No significant difference was found between regions, except for the period 2008-2013; the North compared to the South was associated with a higher probability of EBRT. Men with high-risk localized or locally advanced disease were more likely to receive EBRT instead of RP, compared to intermediate-risk disease. A diagnosis in a university hospital or hospital with radiotherapy department was positively associated with EBRT (only in 2014-2019), as was a diagnosis in a hospital where no RP was performed (both in 2008-2013 and 2014-2019). No association was found with volume of hospital diagnoses.

Table 3. Adjusted odds ratios (OR) of receiving EBRT versus radical prostatectomy in patients with intermediate and high-risk localized and locally advanced prostate cancer in The Netherlands, stratified for diagnoses in 2008-2013 and 2014-2019

OR for receiving EBRT versus radical prostatectomy				
	2008-2013 EBRT N = 12,732, Radical prostatectomy N = 10,924		2014-2019 EBRT N = 14,981, Radical prostatectomy N = 12,054	
	OR [A]	(95%CI)	OR [A]	(95%CI)
Year of diagnosis (continuously)	**0.95**	**(0.94-0.97)**	**1.03**	**(1.01-1.04)**
Age at time of diagnosis, years				
< 65	Reference		Reference	
65 - <75	**3.39**	**(3.08-3.73)**	**2.61**	**(2.26-3.00)**
≥75	**54.03**	**(44.78-65.18)**	**39.33**	**(32.84-47.11)**
Number of comorbidities at diagnosis [B]				
0	Reference		Reference	
1	**1.41**	**(1.18-1.68)**	**1.43**	**(1.18-1.73)**
≥2	**2.17**	**(1.80-2.63)**	**2.24**	**(1.84-2.71)**
Geographical region				
North	Reference		Reference	
East	0.79	(0.58-1.06)	0.91	(0.69-1.19)
South	**0.68**	**(0.48-0.95)**	0.88	(0.65-1.19)
South West	0.77	(0.55-1.07)	0.83	(0.62-1.12)
North West	0.76	(0.57-1.02)	0.85	(0.65-1.11)
Travel time (car) for EBRT, minutes				
<15	Reference		Reference	
15-30	0.90	(0.81-1.00)	**0.91**	**(0.85-0.96)**
>30	**0.85**	**(0.73-0.99)**	**0.88**	**(0.78-0.99)**
Prognostic risk groups				
Intermediate-risk localized	Reference		Reference	
High-risk localized	**2.22**	**(1.92-2.56)**	**1.51**	**(1.33-1.71)**
Locally advanced high-risk	**14.23**	**(12.20-16.59)**	**5.61**	**(4.97-6.33)**

Continued

OR for receiving EBRT versus radical prostatectomy				
	2008-2013 EBRT N = 12,732, Radical prostatectomy N = 10,924		2014-2019 EBRT N = 14,981, Radical prostatectomy N = 12,054	
	OR [A]	(95%CI)	OR [A]	(95%CI)
Type of hospital				
University [C]	Reference		Reference	
Non-university	0.98	(0.65-1.48)	**0.69**	**(0.49-0.97)**
Radiotherapy department embedded in the hospital				
No	Reference		Reference	
Yes	1.22	(0.80-1.87)	**1.42**	**(1.09-1.86)**
Prostatectomies are performed in the hospital				
No	Reference		Reference	
Yes	**0.82**	**(0.67-0.99)**	**0.61**	**(0.50-0.73)**
Volume of intermediate/high-risk localized and locally advanced PCa diagnoses in the hospital [D]				
Low volume	Reference		Reference	
High volume	1.05	(0.80-1.36)	1.13	(0.94-1.35)

OR: odds ratio, EBRT: external beam radiotherapy, 95%CI: 95% confidence interval, PCa: prostate cancer; values in bold are statistically significant

A   Models with both a random intercept and random effect were applied for the analyses on age, number of comorbidities (2014-2019), region (2014-2019), travel time for EBRT (2008-2013), prognostic risk groups and prostatectomies performed in the hospital. The analyses on year of diagnosis, and travel time for EBRT (2014-2019) were not adjusted, as none of the variables fulfilled the criteria for inclusion in the adjustment set. The analyses on number of comorbidities, travel time for EBRT (2008-2013), and prognostic risk group was adjusted for age. The analyses on age, region (2014-2019), volume of diagnoses in the hospital (2008-2013), and prostatectomies performed in the hospital (2014-2019) were adjusted for prognostic risk group. The analysis on region (2008-2013) was adjusted for age and prognostic risk group. The analysis on type of hospital (2008-2013) was adjusted for age and travel time for EBRT. The analyses on type of hospital (2014-2019), and radiotherapy department in the hospital (2014-2019) were adjusted for age and prostatectomies performed in the hospital. The analysis on radiotherapy department in the hospital (2008-2013) was adjusted for age, travel time for EBRT and type of hospital. The analysis on volume of diagnoses in the hospital (2014-2019) was adjusted for prostatectomies performed in the hospital. The analysis on prostatectomies performed in the hospital (2008-2013) was adjusted for year of diagnosis and prognostic risk group. Comorbidities were not included in adjustment sets considering their limited availability. The analysis on type of hospital was not adjusted for a radiotherapy department in the hospital, as this was considered a basic component of university hospitals.

B   Comorbidities were available for patients diagnosed in the South before 2015 and for all patients diagnosed in October 2015-March 2016.

C   Including the single cancer specific hospital in The Netherlands.

D   Patients diagnosed in the 50% of hospitals with the lowest annual average number of intermediate/high-risk localized and locally advanced prostate cancer diagnoses: <75 patients in 2008-2013 and <78 patients in 2014-2019, were categorized in low volume. The remaining patients in the high volume-category.

DISCUSSION

This nationwide study investigating primary radiotherapy in PCa treatment in 2008-2019, showed that EBRT use remained stable in low-risk disease and increased in intermediate/high-risk PCa. Brachy-monotherapy use in low/intermediate-risk PCa decreased. Radiotherapy versus no active treatment were associated with cT, age, number of comorbidities, and region. EBRT versus RP were associated with the year of diagnosis, age, number of comorbidities, travel time for EBRT, prognostic risk, type of hospital, and whether the hospital of diagnosis had a radiotherapy department or RP availability.

Low-risk PCa

The decreasing rates of brachy-monotherapy and RP in low-risk PCa coincided with an increasing percentage of patients who underwent no active treatment. Deferred treatment in low-risk disease is nowadays preferred and similar trends towards no active treatment were observed in the USA, Canada, Australia and Sweden [10,18-20].

Patients with higher cT-classification more often received radiotherapy instead of no active treatment. This trend was also observed in Canada [19] and can be explained by the less favorable outcome with increased probability of disease progression [21]. In case of active treatment, older men most often received EBRT while younger ones more often underwent RP or brachy-monotherapy. Our multilevel analyses also showed that EBRT instead of no active treatment is more often received by older compared to younger men, while brachy-monotherapy instead of no active treatment is mainly given to younger ones. As these analyses did not include RP, mainly younger patients receiving active treatment were excluded. Overall, most elderly patients received no active treatment. The observed distribution of treatment modalities across age groups can be explained by EBRT being non-invasive, contrary to brachytherapy and RP. Similar trends across age groups in low-risk PCa were observed for other Western countries [10-12,19]. Regional variation in the use of radiotherapy versus no active treatment were found, for which reasons remain unclear. In Canada and Sweden, geographical variation in low-risk PCa treatment were also observed [12,19,20] potentially reflecting disparities in available treatment modalities within the regions [19,20]. In Australia, the use of active surveillance

differed between private and public hospitals, possibly related to differences in patient characteristics or hospitals' culture and organization [18]. In our study, however, type of hospital and the treatment modalities available in the diagnosing hospital were not associated with treatment in low-risk PCa in the most recent period.

Intermediate and high-risk PCa

Decreased brachy-monotherapy use in intermediate-risk PCa coincided with increased RP use in 2008-2011, which thereafter decreased, and increased EBRT use in 2014-2019. EBRT and RP also increased in high-risk disease, coinciding decreased non-curative hormonal-monotherapy use. In intermediate and high-risk PCa in the USA and high-risk PCa in Norway, RP use strongly increased as well, although EBRT use remained stable [10,13].

RP is less often considered in advanced disease [22], which is in line with our finding of more frequent EBRT instead of RP in high-risk localized and locally advanced PCa compared to intermediate-risk disease. Nevertheless, current treatment guidelines indicate both EBRT and RP as options in high-risk disease [3-5]. We also found higher age and comorbidities to be associated with a higher likelihood of EBRT versus RP, possibly reflecting treatment decision related to patients' frailty. Similar treatment variation across age groups were seen in Germany and the USA [10,23]. Our analyses further show that the treatment given was associated with the availability of treatment modalities in the diagnosing hospital and with the travel time for EBRT. Also in the UK, the availability of RP and radiotherapy was associated with treatment variation in high-risk PCa; RP was more often applied when available in the diagnosing hospital and patients were more likely to receive brachytherapy following EBRT when brachytherapy was available in the region [24]. Furthermore, in a survey study in the USA, genitourinary oncology physicians' personal level of expertise with brachytherapy was positively associated with the choice for brachytherapy boost [25].

Previous trends and optimal utilization rates

The recent treatment trends in localized PCa differ from trends previously observed in the Netherlands. In 1997-2008, EBRT use decreased, while brachytherapy use increased [9]. Furthermore, decreased use of no active

treatment and increased RP use were observed in 1989-2006 [14]. Differences in treatment over time can partly be explained by changed treatment guidelines recommending active surveillance in low-risk PCa [3-6], and may further be caused by the changed availability of radiotherapy and RP. For locally advanced disease, an increasing trend in EBRT was already observed for 1997-2008 [9].

Thompson et al. previously modelled a guideline-based optimal EBRT utilization rate of 51% in patients with PCa in Western countries [26]. However, for all non-metastatic PCa combined, we observed primary and adjuvant EBRT utilization rates of 28% and 1%, respectively. Specifically the modelled rate of EBRT following RP is much higher than the utilization rate observed. The differences may be explained by the modelling study including EBRT in metastatic disease and not addressing the prevalence of prognostic risk groups and treatment protocols in The Netherlands. For RP and brachytherapy, observed (27% and 8%, respectively) and modelled optimal rates (24% and 9%, respectively) were comparable [26], as was our observed primary EBRT rate with observations from Norway in 2006-2015 (26%) and the USA in 2004-2014 (27%-29%) [10,13]. Future research should further explore the similarities and disparities of radiotherapy use in prostate cancer treatment across Western/European countries.

Strengths and limitations

Strengths of our study include using nationwide population-based data and providing a unique overview of radiotherapy use in non-metastatic PCa in The Netherlands for 12 recent years. Limitations include not being able to distinguish active surveillance from watchful waiting. Nevertheless, patients receiving no active treatment, having low or intermediate-risk PCa and no limited life expectancy, most likely were managed with active surveillance, while watchful waiting was more likely in the other patients. Also no distinction could be made between conventional and robot-assisted RP, as surgical techniques performed were limitedly registered in our study period. Furthermore, the analyses could not be adjusted for comorbidities given their limited availability. This may have resulted in residual confounding, especially in associations found for age. In patients who underwent RP before 2013, the pretreatment assessment of prognostic risk may be over- or (to a lesser extent) underestimated [27] in our study, because only resection specimen-based GS were available at that time. Changed diagnostic procedures, including targeted biopsies, MRI and PSMA-PET scans [28], furthermore improved staging in the

study period. Consequently, stage shifts occurred which probably changed the overall distribution of treatments applied. For the reported treatment trends stratified for risk groups, however, no major changes due to improved diagnostic procedures are expected. Finally, variation in prognostic risk group classification exists within The Netherlands, causing differences in risk group assessment between our study and some Dutch hospitals.

Conclusions

Over time, an increasing percentage of patients with intermediate and high-risk PCa received curative-intent treatment. EBRT gained a more prominent place in treatment of intermediate/high-risk PCa, while use of brachy-monotherapy in intermediate-risk PCa diminished. RP was increasingly applied in high-risk PCa. Specific groups of patients and those diagnosed in hospitals with a radiotherapy department or where no RPs were performed, more likely received EBRT instead of RP. This variation suggests both treatment decision related to patients and disease characteristics and to the availability of treatment modalities in the hospitals of diagnosis. In low-risk PCa, more patients refrained from active treatment. EBRT use remained limited and the use of brachy-monotherapy and RP decreased. Variation in use of radiotherapy instead of no active treatment suggests that the choice for active treatment with EBRT/brachy-monotherapy is related to patient and tumor characteristics. No variation was observed for hospital characteristics in the most recent period, suggesting adherence to the recommendation of deferred treatment irrespective of the treatment modalities available.

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6

CHAPTER

7

Chemoradiation in locally
advanced rectal cancer

TRENDS AND VARIATION IN THE USE OF RADIOTHERAPY IN NON-METASTATIC RECTAL CANCER: A 14-YEAR NATIONWIDE OVERVIEW FROM THE NETHERLANDS

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ABSTRACT

Purpose and background:

This study describes nationwide primary radiotherapy utilization trends for non-metastasized rectal cancer (RC) in the Netherlands in 2008-2021. In 2014, both colorectal cancer screening and a new guideline specifying prognostic risk groups for neoadjuvant treatment were implemented.

Methods:

Patients with non-metastasized RC in 2008-2021 (N=37,510) were selected from the Netherlands Cancer Registry and classified into prognostic risk groups. Treatment was studied over time and age. Multilevel logistic regression analyses were performed to identify factors associated with 1) radiotherapy versus chemoradiotherapy use for intermediate RC and 2) chemoradiotherapy without versus with surgery for locally advanced RC.

Results:

For early RC, use of neoadjuvant radiotherapy decreased (15% to 5% between 2008-2021), while use of endoscopic resections increased (8% in 2015, 17%, in 2021). In intermediate-risk RC, neoadjuvant chemoradiotherapy (43% until 2011, 25% in 2015) shifted to radiotherapy (42% in 2008, 50% in 2015), the latter being most often applied in older patients. In locally advanced RC, use of chemoradiotherapy without surgery increased (2-4% in 2008-2013, 17% in 2019-2021). Both neoadjuvant treatment in intermediate disease and omission of surgery following CRT in locally advanced disease varied with increasing age (OR>75vs<50: 2.17(95%CI:1.54-3.06)) and treatment region (Southwest and Northwest OR 0.63(95%CI:0.42-0.93) and 0.65(95%CI:0.44-0.95), respectively, compared to North).

Conclusion:

Treatment patterns in non-metastasized RC significantly changed over time. Both effects of the national screening program and new treatment guideline were apparent, as well as a paradigm shift towards organ preservation (watch-and-wait). Observed regional variations may indicate adoption differences regarding new treatment strategies.

INTRODUCTION

Colorectal cancer is the third most common cancer type globally, and the second leading cause of cancer mortality. Approximately one third of colorectal cancer cases regards rectal cancer.

Surgery is standard treatment for rectal cancer, with a decreased risk of locoregional recurrence when the mesorectal fat including the mesorectal fascia (MRF) is resected along with the tumor[1–3] (total mesorectal excision (TME)). Preoperative (chemo)radiotherapy may further decrease the locoregional recurrence risk[3–5], and a waiting period of several weeks between the completion of (chemo)radiotherapy and surgery enables downstaging of the tumor and lymph node status[5,6]. For patients with tumors reaching towards the MRF or other organs, downstaging could be essential to reduce the risk for an irradical resection. Several international guidelines exist for (neoadjuvant) treatment of rectal cancer, but global differences in treatment are apparent due to lack of evidence or equipoise. From 2008 onwards in the Netherlands, the indications for neoadjuvant (chemo)radiotherapy have become specified. Neoadjuvant radiotherapy was advised for cT2-4N0-1/XM0 rectal cancer, and neoadjuvant chemoradiotherapy in case of an involved MRF (≤1mm margin between the tumor and the MRF) or ≥4 clinically positive lymph nodes. A new Dutch guideline was released in 2014, in which neoadjuvant treatment in early rectal cancer (cT1-3bN0-XM0) was no longer advised. Furthermore, specifications were given for the use of neoadjuvant radiotherapy (intermediate disease: cT1-3N1/cT3c-d; uninvolved MRF) and chemoradiotherapy (locally advanced disease: cT4, or cT3 with involved MRF, and/or cN2/extramesorectal pathological lymph nodes). Table 1 summarizes the Dutch guidelines regarding (chemo)radiotherapy for rectal cancer, largely based on MRI staging.

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Table 1. The Dutch guideline for neoadjuvant (chemo)radiotherapy for patients with non-metastasized rectal cancer

Date national guideline	TNM classification*	Neoadjuvant treatment
2008-2014	cT1N0	None
	cT2-4 N0/N1, and distance to MRF > 1 mm	5 x 5 Gy preoperative radiotherapy
	Distance to MRF ≤1mm or cN2	Preoperative chemoradiotherapy
2014- onwards	cT1-2N0 or cT3a-bN0; distance to MRF >1mm	None
	cT1-3N1 or cT3c-d; distance to MRF >1mm	5 x 5 Gy preoperative radiotherapy
	cT4 or cT3 with distance to MRF ≤1mm and/or cN2/extramesorectal pathological lymph nodes	Preoperative chemoradiotherapy

MRF = mesorectal fascia
*as staged on MRI/endorectal ultrasound for 2008-2014 and MRI for 2014 onwards

Over the years, MRI has become a crucial tool in adequate staging as well as response evaluation and surveillance for rectal cancer. Furthermore, the MRI allows for selection of patients who may benefit from neoadjuvant treatment and which do not.

In a selection of patients who received neoadjuvant (chemo)radiotherapy, a pathological complete response is seen at the time of surgery [5,7]. This led to the introduction of the organ-sparing "watch and wait" (W&W)-concept, in which surgery is delayed and sometimes even omitted in case of a clinical complete response[8]. Interest in this strategy has grown over the years and the strategy is monitored in the national W&W program as well as the International W&W Database. Also, treatment intensification strategies have been introduced to increase the probability of a clinical complete response, including offering localized dose escalation or the addition of systemic treatment before or after (chemo)radiotherapy.

The changing treatment guidelines and growing interest in organ-sparing treatment changed the treatment patterns for rectal cancer in the Netherlands. Furthermore, a nationwide screening program for colorectal cancer was gradually implemented in the period 2014-2019 for people aged 55-75 years. This led to the detection/removal of premalignant lesions and/or asymptomatic tumors and changed the stage distribution of rectal cancer. Along with a

decreased incidence of rectal cancer, it further changed the radiotherapy treatment patterns in rectal cancer over the years. Some publications have provided an overview of radiotherapy use in rectal cancer treatment in the Netherlands, but a nationwide comprehensive overview focused on the trends and variation in radiotherapy use in non-metastasized rectal cancer treatment including data up to 2021 is lacking[9–12]. This nationwide study therefore aims to investigate trends and variation in the use of radiotherapy in the broader context of non-metastasized rectal cancer treatment in the Netherlands between 2008 and 2021, with stratification for early, intermediate risk and locally advanced disease.

MATERIALS AND METHODS

Study population

Patients diagnosed with cT1-4N0/XM0 and cTXN1-2M0 rectal cancer in 2008-2021 were selected from the Netherlands Cancer Registry (NCR). The NCR includes information on patient, disease and primary treatment of all diagnosed with cancer in the Netherlands. The data from the NCR is extracted by trained registrars from patients' medical records in all Dutch hospitals.

Definitions

The clinical T-, N- and M-stages were coded according to TNM6 (2008-2009), TNM7 (2010-2016) and TNM8 (2017-2021). Clinically involved MRF data was registered from 2015 and subclassification of cT3 stage (related to the extent of extramural invasion) was available from 2018. The resulting missing information in earlier years called for an alternative prognostic risk group-classification: early rectal cancer was defined as cT1-2N0/XM0 and intermediate rectal cancer as cT1-3/XN1M0. Patients with cT3N0/XM0 were randomly assigned to the early or intermediate risk group, keeping the actual proportion of cT3N0 (with known extramural invasion) in both groups intact: 81.5% in the early group, 18.5% in the intermediate group. Locally advanced rectal cancer was defined as cT4 and/or cN2 in the alternative classification. Supplementary Table 1 defines and numericizesthis alternative classification. Patients who could not be stratified into a risk group because of incomplete TNM-information (cTXNX or cTXN0) were excluded from this study (N=5877).

Patients' comorbidities at the time of diagnosis were available for the South-region only until 2015 and thereafter for a limited number of patients. Comorbidities were classified based on the Charlson Comorbidity Index-categories (CCI, see Supplementary Table 2). WHO Performance Status was available from 2015.

Treatment modalities analyzed included short course radiotherapy, chemoradiotherapy, other radiotherapy, chemotherapy, surgery and endoscopic resection.

Minimal travel time for radiotherapy was stratified (<15, 15-30, and >30 minutes). The hospital in which the patient was diagnosed was classified 1) according to type, 2) whether a radiotherapy department constituted a part, and 3) into three equal groups according to its annual number of non-metastasized rectal cancer diagnoses: low (≤22), intermediate (23-41) or high volume (≥42 patients). Regional variation was investigated by dividing the Netherlands into five regions according to patients' residence: North, East, South, Southwest, and Northwest (Supplementary Figure 1).

Analyses

Patient, disease, and hospital characteristics were presented and stratified into the various risk groups. Treatment trends for early, intermediate, and locally advanced rectal cancer were described over time and by age groups with 5-year intervals, except for 70-75 years (to prevent separation of screening ages into different groups). Age groups with <50 patients were not presented. For the stratification into the risk groups the alternative classification was used. To validate this classification, trends in treatment in 2015-2021 were also described for early, intermediate, and locally advanced rectal cancer using the original classification (Supplementary Figures 2-4).

In the supplementary material, the evolution of stage distribution, use of endoscopic resection, chemoradiation without surgery , and radiotherapy versus chemoradiotherapy were shown, the latter both overall and stratified for each region. In addition, treatment of locally advanced rectal tumors were displayed stratified for the regions.

Multilevel logistic regression analyses were performed to identify factors associated with 1) application of radiotherapy versus chemoradiotherapy

for intermediate rectal cancer, stratified for diagnoses before and since 2014 to distinguish older from more recent years, and 2) application of chemoradiotherapy not followed by surgery versus chemoradiotherapy followed by surgery for locally advanced rectal cancer diagnosed since 2014. Diagnoses before 2014 were excluded, given the then limited use of chemoradiotherapy without surgery. The analyses on chemoradiotherapy with/without surgery were repeated in a sensitivity analysis including only a subset of patients younger than 70 years (reported in the supplementary), to exclude older patients who may have been omitted from surgical treatment due to frailty.

Multilevel analyses correct for nesting of patients within hospitals. For each association investigated in the analyses, distinct models were created. A model included a random effect and random intercept for the hospital-level if the corrected Akaike Information Criterion (AICc), a mathematical method for evaluating how well a model fits the data)- improved compared to the model with only a random intercept. For each investigated association, a set of variables for adjustment was selected. When univariable inclusion resulted in at least 5 % change in the odds ratio (OR) of interest compared to the unadjusted multilevel OR, a variable was included in the adjustment set. Ninety-five percent confidence intervals (95 %CI) were calculated and reflect probable OR-estimates. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

In total, 37,510 patients were diagnosed with early (44%), intermediate (30%), and locally advanced (25%) rectal cancer from 2008-2021. The proportion of early disease increased since 2014 (Supplementary Figure 5). Disease, patient, and hospital characteristics were comparably distributed for the various risk groups (Table 2). Roughly 70% of patients diagnosed with early, intermediate, and locally advanced rectal cancer fell into the 50-75 years age group. Of all patients, 63% was male. For all prognostic risk groups, but mainly for intermediate and locally advanced rectal cancer, the absolute incidence decreased after 2015.

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Table 2. Disease, patient and hospital characteristics, for patients diagnosed with non-metastatic rectal cancer in the Netherlands, stratified for early, intermediate and locally advanced disease (N=37,510)

	Early		Intermediate		Locally advanced	
	N = 16,669		N = 11,291		N = 9,550	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*
Clinical T-stage						
TX	n/a		514	(4.6)	112	(1.2)
T1	3,432	(20.6)	176	(1.6)	19	(0.2)
T2	6,875	(41.2)	1,854	(16.4)	462	(4.8)
T3	6,362	(38.2)	8,747	(77.5)	5,136	(53.8)
T4	n/a		n/a		3,821	(40.0)
Clinical N-stage						
NX	1,801	(10.8)	170	(1.5)	272	(2.8)
N0	14,868	(89.2)	1,284	(11.4)	1,000	(10.5)
N1	n/a		9,837	(87.1)	1,190	(12.5)
N2	n/a		n/a		7,088	(74.2)
Year of diagnosis						
2008-2012	4,948	(29.7)	3,603	(31.9)	2,821	(29.5)
2013-2017	6,642	(39.8)	4,813	(42.6)	4,349	(45.5)
2018-2021	5,079	(30.5)	2,875	(25.5)	2,380	(24.9)
Sex						
Men	10,547	(63.3)	7,274	(64.4)	5,637	(59.0)
Women	6,122	(36.7)	4,017	(35.6)	3,913	(41.0)
Age at time of diagnosis						
<50 years	645	(3.9)	663	(5.9)	890	(9.3)
50-75 years	11,724	(70.3)	7,896	(69.9)	6,620	(69.3)
>75 years	4,300	(25.8)	2,732	(24.2)	2,040	(21.4)
Region of residence						
North	2,292	(13.8)	1,495	(13.2)	1,346	(14.1)
East	2,688	(16.1)	1,953	(17.3)	1,964	(20.6)
South	4,208	(25.2)	2,677	(23.7)	2,481	(26.0)
Southwest	3,602	(21.6)	2,438	(21.6)	1,673	(17.5)
Northwest	3,879	(23.3)	2,728	(24.2)	2,086	(21.8)
Comorbidities assessed [A]	5,689	(34.1)	3,625	(32.1)	3,394	(35.5)
No comorbidity in any CCI category	2,988	(52.5)	2,005	(55.3)	2,007	(59.1)
Comorbidities in 1 CCI category	1,650	(29.0)	985	(27.2)	912	(26.9)
Comorbidities in ≥2 CCI categories	1,051	(18.5)	635	(17.5)	475	(14.0)
Most frequent comorbidities						
Diabetes Mellitus	827	(14.5)	566	(15.6)	479	(14.1)
Chronic Pulmonary Disease	622	(10.9)	397	(11.0)	328	(9.7)
Other malignancy	649	(11.4)	366	(10.1)	287	(8.5)

Continued

	Early		Intermediate		Locally advanced	
	N = 16,669		N = 11,291		N = 9,550	
	n	(%)	n	(%)	n	(%)
WHO performance status available [B]	4,461	(26.8)	3,624	(32.1)	3,739	(39.2)
Performance status 0	2,997	(67.2)	2,288	(63.1)	2,112	(56.5)
Performance status 1	1,130	(25.3)	1,057	(29.2)	1,287	(34.4)
Performance status 2-4	334	(7.5)	279	(7.7)	340	(9.1)
Minimal travel time for radiotherapy						
<15 minutes	5,892	(35.3)	3,892	(34.5)	3,318	(34.7)
15-30 minutes	9,108	(54.6)	6,259	(55.4)	5,310	(55.6)
>30 minutes	1,669	(10.0)	1,140	(10.1)	922	(9.7)
Diagnosed in a university hospital [C D]	975	(5.9)	570	(5.1)	631	(6.6)
Radiotherapy as part of the diagnosing hospital [C]	2,918	(17.5)	1,967	(17.4)	1,844	(19.3)
Volume in the hospital of diagnosis [C E]						
Low volume of diagnoses	2,316	(13.9)	1,637	(14.5)	1,346	(14.1)
Intermediate volume of diagnoses	4,880	(29.3)	3,272	(29.0)	2,839	(29.7)
High volume of diagnoses	9,457	(56.8)	6,369	(56.5)	5,360	(56.2)

CCI: Charlson Comorbidity Index; n/a: not applicable

A   Before 2015, comorbidities were only assessed for patients diagnosed in the South region.

B   Available only since 2015.

C   Hospital of diagnosis is missing for 34 patients.

D   Including the single cancer-specific hospital in the Netherlands.

E   The one third of hospitals with the lowest number of M0 rectal cancer diagnoses (average ≤22 p/year) were classified as low volume, the one third of hospitals with the highest number of M0 rectal cancer diagnoses (average ≥42 p/year) were classified as high volume, the other one third of hospitals were classified as intermediate volume.

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Supplementary Figures 6A-F show the overall use of radiotherapy versus chemoradiotherapy over time, overall as well as separately per region.

In early rectal cancer, use of neoadjuvant radiotherapy followed by surgery decreased from 61% to 7% in the years between 2008 and 2021, and neoadjuvant chemoradiotherapy followed by surgery decreased from 15% to 5% in this period. (Figure 1A) The application of surgery without neoadjuvant treatment increased from 14% to 71% between 2008 and 2015. After 2015, this number decreased to 59%, coinciding with the increase in endoscopic resections (8% in 2015, 17% in 2021). For all ages ≤85, surgery without neoadjuvant (chemo) radiotherapy was the most frequently applied treatment (Figure 1B). In the age

groups eligible for screening, the proportion of patients receiving endoscopic resections (10%) or surgery without neoadjuvant (chemo)radiotherapy (50%) was highest, while neoadjuvant radiotherapy was used least (39%).
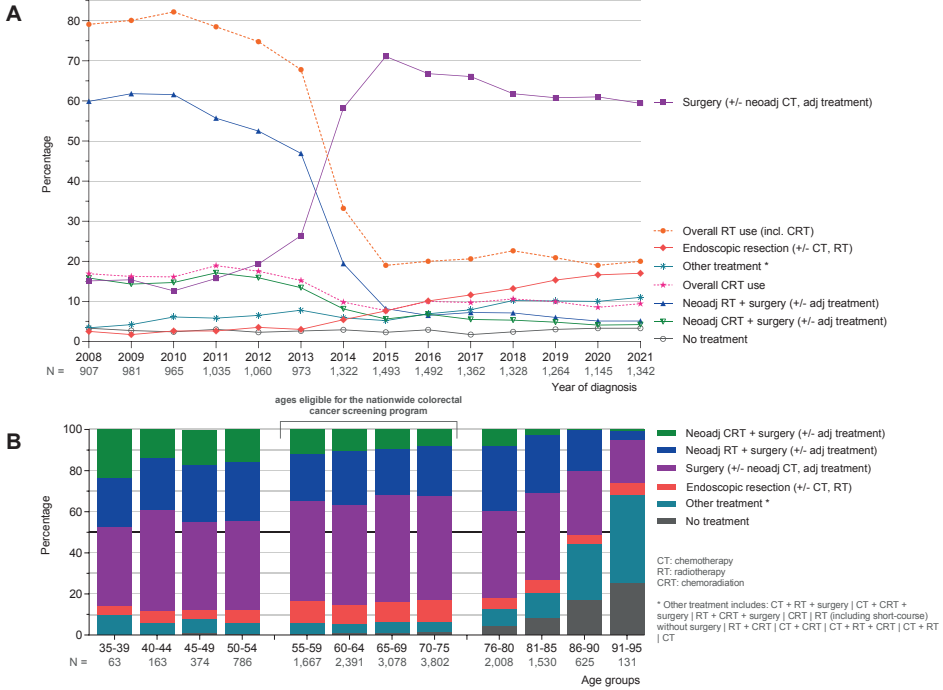
Figure 1. Treatments for early rectal cancer A) over time, B) according to age groups

In intermediate rectal cancer, there appears to be a shift in 2008-2015 from neoadjuvant chemoradiotherapy followed by surgery (43% until 2011, 25% in 2015) to neoadjuvant radiotherapy followed by surgery (42% in 2008, 50% in 2015) (Figure 2A). Chemoradiotherapy without surgery was increasingly applied between 2015 and 2018 (2-10%), as well as short-course radiotherapy without surgery. With increasing age, (chemo)radiotherapy use decreased and patients more often underwent surgery without neoadjuvant treatment (6-10% for ages 35-49, 17% for ages 81-90) (Figure 2B). Younger patients more often received neoadjuvant chemoradiotherapy followed by surgery, while older patients more often received neoadjuvant radiotherapy followed by surgery.
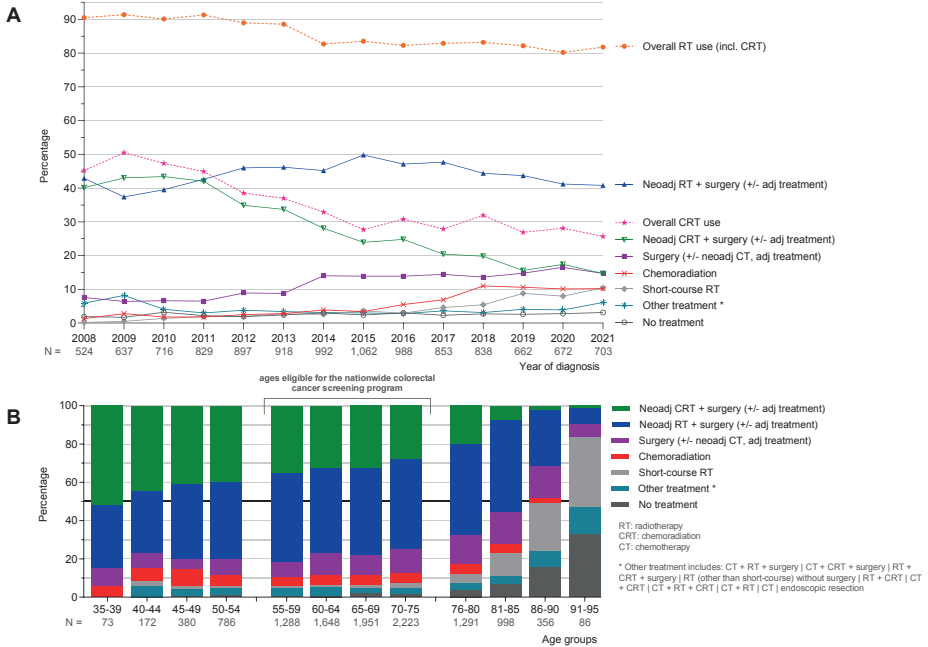
Figure 2. Treatments for intermediate rectal cancer A) over time, B) according to age groups

A marked expansion of the "Other treatment" category is evident for the more advanced age groups in all risk groups, predominantly accounted for by an increase in less invasive treatment (predominantly short course radiotherapy without surgery) in this population.

Variations in the application of radiotherapy versus chemoradiotherapy for intermediate rectal cancer are shown in Table 3, stratified according to period. Patients at older ages were more likely to receive neoadjuvant radiotherapy instead of chemoradiation, as the ORs for ages >75 compared to <50 years demonstrate (in 2008-2013: OR:7.02; 95%CI:5.22-9.45, in 2014-2021: OR:3.54; 95%CI:2.72-4.61). In 2008-2013, use of radiotherapy versus chemoradiation was higher for more recent years and for the Northwest compared to the North-region (OR:1.44; 95%CI:1.01-2.06). Patients with comorbidity in ≥2 versus 0 category and those with a performance status of 2-4 versus 0 had a higher probability of receiving radiotherapy compared to chemoradiotherapy.

Table 3. Adjusted odds ratios (OR) of receiving radiotherapy (RT) versus chemoradiation (CRT) (with or without induction/consolidation RT), stratified for patients diagnosed with intermediate rectal cancer before 2014 (N=4,058) and since 2014 (N=5,581) in the Netherlands

	Diagnosed before 2014		Diagnosed since 2014	
	RT, N = 2,106		RT, N = 3,604	
	CRT, N = 1,952		CRT, N = 1,977	
	OR [A]	(95%CI)	OR [B]	(95%CI)
Year of diagnosis (continuously)	**1.12**	**(1.08-1.16)**	1.03	(1.00-1.05)
Sex				
Men	Reference		Reference	
Women	1.14	(0.99-1.31)	1.04	(0.93-1.17)
Age at time of diagnosis				
< 50 years	Reference		Reference	
50-75 years	**1.75**	**(1.35-2.26)**	**1.56**	**(1.24-1.98)**
> 75 years	**7.02**	**(5.22-9.45)**	**3.54**	**(2.72-4.61)**
Region of residence				
North	Reference		Reference	
East	1.30	(0.90-1.86)	1.08	(0.79-1.48)
South	0.96	(0.66-1.38)	0.99	(0.72-1.36)
Southwest	0.71	(0.49-1.02)	0.97	(0.71-1.33)
Northwest	**1.44**	**(1.01-2.06)**	1.34	(0.99-1.83)
Comorbidities [C]				
No comorbidity in any CCI category	n/a		Reference	
Comorbidity in 1 CCI category	n/a		1.24	(0.97-1.59)
Comorbidity in ≥2 CCI categories	n/a		**1.48**	**(1.11-1.98)**
WHO performance status [D]				
Performance status 0	n/a		Reference	
Performance status 1	n/a		1.04	(0.88-1.23)
Performance status 2-4	n/a		**3.17**	**(2.15-4.66)**
Hospital of surgery				
Non-university	Reference		Reference	
University [E]	1.17	(0.74-1.84)	1.43	(0.99-2.08)
Volume in the hospital of surgery [F]				
Low volume of diagnoses	Reference		Reference	
Intermediate volume of diagnoses	1.07	(0.75-1.53)	0.91	(0.69-1.19)
High volume of diagnoses	1.18	(0.83-1.66)	1.03	(0.78-1.35)

Continued

OR: odds ratio, RT: radiotherapy, CRT: chemoradiation, 95%CI: 95%% confidence interval, CCI: Charlson Comorbidity Index; values in bold are statistically significant

A   Multilevel logistic regression models with both a random intercept and random effect were not applied. The analyses on year of diagnosis, age, region and volume of diagnosis were not adjusted, as none of the variables fulfilled the criterium for inclusion in the adjustment sets. The analysis on sex was adjusted for age. The analysis on type of hospital was adjusted for region and volume of diagnosis.

B   A multilevel logistic regression model with both a random intercept and random effect was applied for number of comorbidities. The analyses on year of diagnosis, sex and age were not adjusted, as none of the variables fulfilled the criterium for inclusion in the adjustment sets. The analyses on region, number of comorbidities, performance status and type of hospital were adjusted for age. The analysis on volume of diagnosis was adjusted for type of hospital. NB. number of comorbidities and performance status were not included in adjustment sets, considering their limited availability.

C   Comorbidities were assessed for 2,395 (43%) of the patients diagnosed since 2014.

D   WHO performance status was available for 3,138 (56%) of the patients diagnosed since 2014.

E   Including the single cancer specific hospital in the Netherlands.

F   The one third of hospitals with the lowest number of M0 rectal cancer diagnoses (average ≤22 p/year) were classified as low volume, the one third of hospitals with the highest number of M0 rectal cancer diagnoses (average ≥42 p/year) were classified as high volume, the other one third of hospitals were classified as intermediate volume.

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In locally advanced rectal cancer, overall radiotherapy use (including chemoradiotherapy) remained stable over time (91%) (Figure 3A). The use of neoadjuvant chemoradiotherapy followed by surgery decreased from 61% until 2016 to 40% in 2021, while chemoradiotherapy without surgery was increasingly applied (2-4% until 2013, 17% in 2019-2021). The use of neoadjuvant chemotherapy followed by chemoradiotherapy and surgery increased slightly since 2016, while short-course radiotherapy use followed by chemotherapy with/without surgery increased greatly from 1% in 2019 to 13% in 2021. Chemoradiotherapy was less often applied with increasing age (Figure 3B). Older patients more often received surgery with neoadjuvant radiotherapy than younger patients (7% for ages 40-44, 29% for ages 81-85), while younger patients more often received neoadjuvant chemoradiotherapy than older patients (74% vs 20%, respectively).
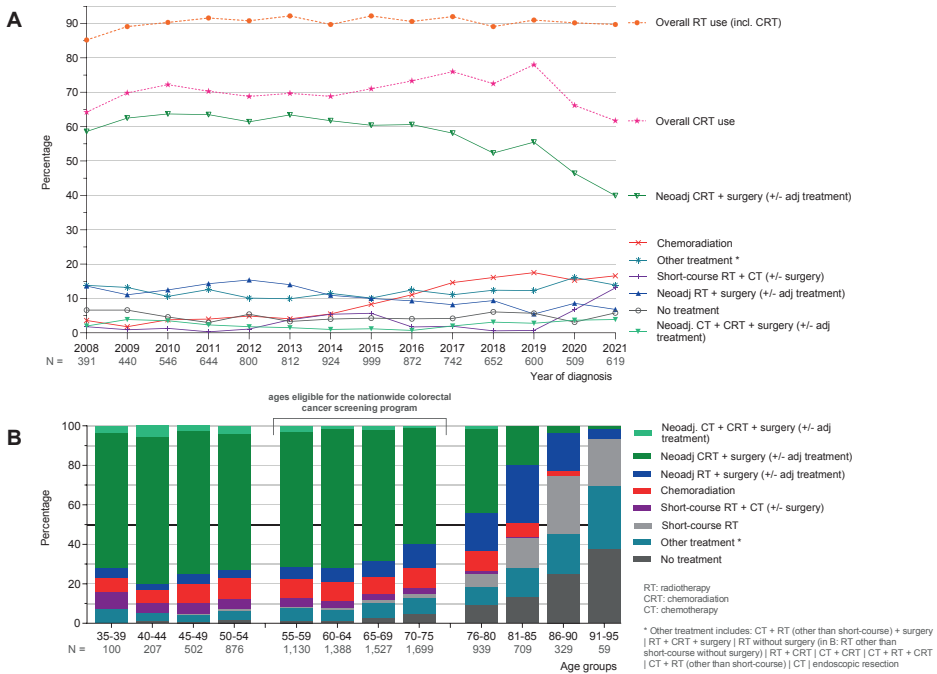
Figure 3. Treatments for locally advanced rectal cancer A) over time, B) according to age groups

Supplementary Figures 7A-E show the trends in therapies for patients with locally advanced rectal cancer separated per region.

Table 4 shows variation in application of neoadjuvant chemoradiotherapy without versus with surgery for locally advanced rectal cancer after 2014. Increased application of chemoradiotherapy without surgery is demonstrated by the OR of 1.21 (95%CI:1.17-1.26) for each more recent year. Compared to patients aged <50 years, older patients were more likely to receive chemoradiotherapy without surgery (OR 50-75 years:1.40; 95%CI:1.05-1.87, and OR >75 years:2.17; 95%CI:1.54-3.06). Patients living in the Southwest and Northwest, compared to the North, were less likely to have surgery omitted following chemoradiotherapy.

Table 4. Adjusted odds ratios (OR) of receiving chemoradiation (CRT) without surgery versus CRT with surgery, for patients diagnosed with locally advanced rectal cancer since 2014 in the Netherlands (N=4,019)

	Diagnosed since 2014	
	CRT without surgery, N = 730	
	CRT, N = 3,289	
	OR [A]	(95%CI)
Year of diagnosis (continuously)	**1.21**	**(1.17-1.26)**
Sex		
Men	Reference	
Women	0.89	(0.76-1.06)
Age at time of diagnosis		
< 50 years	Reference	
50-75 years	**1.40**	**(1.05-1.87)**
> 75 years	**2.17**	**(1.54-3.06)**
Region of residence		
North	Reference	
East	0.84	(0.59-1.21)
South	0.74	(0.50-1.09)
Southwest	**0.63**	**(0.42-0.93)**
Northwest	**0.65**	**(0.44-0.95)**
Comorbidities [B]		
No comorbidity in any CCI category	Reference	
Comorbidity in 1 CCI category	0.99	(0.68-1.43)
Comorbidity in ≥2 CCI categories	1.56	(1.00-2.44)
WHO performance status [C]		
Performance status 0	Reference	
Performance status 1	0.88	(0.71-1.08)
Performance status 2-4	**1.55**	**(1.02-2.36)**
Hospital of surgery		
Non-university	Reference	
University [D]	1.46	(0.92-2.33)
Volume in the hospital of surgery [E]		
Low volume of diagnoses	Reference	
Intermediate volume of diagnoses	1.42	(0.97-2.08)
High volume of diagnoses	1.42	(0.97-2.08)

OR: odds ratio, CRT: chemoradiation, 95%CI: 95%% confidence interval, CCI: Charlson Comorbidity Index; values in bold are statistically significant

A   A multilevel logistic regression models with both a random intercept and random effect was applied for number of comorbidities. The analyses on year of diagnosis, sex and region were not adjusted, as none of the variables fulfilled the criterium for inclusion in the adjustment sets. The analysis on age was adjusted for year of diagnosis. The analyses on number of comorbidities and performance status were adjusted for age. The analysis on type of hospital was adjusted for year of diagnosis, region and volume of diagnosis. The analysis on volume of diagnosis was adjusted for type of hospital. NB. number of comorbidities and performance status were not included in adjustment sets, considering their limited availability.

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Continued

B   Comorbidities were assessed for 1,835 (46%) of the patients diagnosed since 2014.

C   WHO performance status was available for 2,718 (68%) of the patients diagnosed since 2014.

D   Including the single cancer specific hospital in the Netherlands.

E   The one third of hospitals with the lowest number of M0 rectal cancer diagnoses (average ≤22 p/year) were classified as low volume, the one third of hospitals with the highest number of M0 rectal cancer diagnoses (average ≥42 p/year) were classified as high volume, the other one third of hospitals were classified as intermediate volume.

DISCUSSION

This nationwide study investigated radiotherapy use in primary non-metastasized rectal cancer treatment from 2008-2021. For early rectal cancer, less neoadjuvant treatment was given, and more endoscopic resections occurred. For intermediate rectal cancer, neoadjuvant chemoradiotherapy shifted to neoadjuvant radiotherapy. For patients with locally advanced rectal cancer, an increase was seen in the application of chemoradiotherapy without surgery.

These observed trends reflect both the new treatment guideline and the introduction of the national screening program for colorectal cancer in 2014. The latter led to reduced incidence of rectal cancer, changed prognostic risk group distribution, and the increased application of endoscopic resections by the gastroenterologist for early rectal cancer, which coincided with relative declining use of surgical treatment.

Changing neoadjuvant treatment

In the years preceding the scope of this study, radiotherapy for rectal cancer was given either preoperatively or postoperatively. During 1997-2008, radiotherapy use increased in the Netherlands, predominantly the preoperative use, as the Dutch TME-trial proved pre-operative radiotherapy to be effective in reducing the local recurrence risk.[13]. The national guideline published in 2008 subsequently advised pre-operative radiotherapy for cT2-4N0-1 disease.[14]. The new national guideline, published in 2014, no longer advised neoadjuvant radiotherapy for cT1-3b tumors, which resulted in a clear decrease in neoadjuvant radiotherapy use for early rectal cancer as shown in our study.

We observed a decline in the use of neoadjuvant chemoradiotherapy and increase in neoadjuvant radiotherapy in 2008-2014 for intermediate rectal

cancer, which may result from the general belief that de-escalation of neoadjuvant treatment for this group (in line with the existing guideline) was warranted. Also, the definition of involved MRF became more strict over time, resulting in less patients considered having MRF involved disease and therefore being indicated for receiving neoadjuvant chemoradiotherapy. As our intermediate group could include MRF involved disease, this may also have contributed to the shift towards neoadjuvant radiotherapy instead of chemoradiotherapy.

In intermediate disease, we found older and more frail patients to be more likely to receive the less intensive neoadjuvant radiotherapy than neoadjuvant chemoradiation. The regional difference found only in 2008-2013, may indicate early adoption of neoadjuvant radiotherapy instead of neoadjuvant chemoradiation.

Organ-preservation

Several studies report a pathological complete response rate of 10-20% after neoadjuvant chemoradiotherapy for patients with locally advanced rectal cancer[5,7]. For these patients, a watch-and-wait policy can be introduced in an attempt to prevent, or at least delay, surgical treatment[15]. This non-surgical management has received growing interest of patients who want to avoid the risks of surgery and preserve their rectum. This paradigm shift towards organ preservation is also illustrated in the current study. Use of chemoradiotherapy not followed by surgery increased for locally advanced rectal cancer, and use of chemoradiotherapy for younger patients with intermediate rectal cancer has increased, illustrating the pursuit for organ preservation.

For locally advanced rectal cancer diagnosed since 2014, we found older and frailer patients (having a worse performance status) more likely to have surgery omitted following chemoradiation. The regional variation found for chemoradiotherapy without versus with surgery possibly indicate differences in adoption or belief of organ-preserving treatment. In the sensitivity analysis (Supplementary Table 3), excluding patients aged ≥70 at the aim of excluding those who may have been omitted from surgical treatment due to frailty, chemoradiation without surgery was also less likely applied in the South compared to the North-region, as well as in non-university compared to university hospitals. The latter possibly reflects university hospitals to be the

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first to adopt innovative treatment choices – at least for younger patients. In the Netherlands, ongoing studies such as the TESAR and international STAR-TREC phase II-III trials [16] [17] aim to provide more insight into appropriate patient selection for organ preservation.

Several strategies are being explored to potentially improve the chance of a complete response, including increasing the total radiotherapy dose[18]. Providing dose escalation through external beam radiotherapy increases the risk of complications, however[19–21]. The findings of amongst others the OPERA trial has led to the justification in international guidelines of endoluminal contact brachytherapy as a feasible option for organ preservation in early rectal tumors.[22][23] The challenge in the upcoming years will remain performing adequate patient selection for a potential organ-sparing pathway. Unfortunately, dose escalation has not yet been specified as a registered item in the NCR for our study period and could therefore not be evaluated. The addition of systemic treatment before or after (chemo)radiotherapy is another strategy that may improve the complete response chance. Adding chemotherapy may have a more significant role in the prevention of systemic disease for patients with rectal cancer[24–28]. Short course radiotherapy followed by chemotherapy (CAPOX or FOLFOX) before TME in locally advanced rectal cancer increased pathological response, compared to chemoradiotherapy (RAPIDO study) [29]. In the current study, a surge in the application of the "RAPIDO" treatment scheme for patients with locally advanced is apparent since 2019 , corresponding to the time when the trial-results became widespread. However, concerns regarding toxicity of the RAPIDO-regimen not outweighing the potential benefits may limit the use of this scheme in the future years.

For future research, it would be insightful to study the consequences of the observed shift in treatment trends on oncologic outcomes.

In the current study, de-escalation of treatment is seen in those aged >80. This is not surprising, considering the potential risks of surgical, radiotherapeutic and systemic treatment for this (often) frail population. The elderly frail population with rectal cancer entail a heterogeneous group for which no standardized treatment protocol is suitable, rendering decision-making challenging. Nevertheless, refraining from treatment ultimately leads to tumor progression and often debilitating symptoms. Multidisciplinary evaluation including geriatric assessment may prove useful in defining the best suitable treatment.

Short course therapy followed by a waiting period may allow for an eventual R0 resection[6,30]. For patients who are inoperable or refuse surgery, palliative radiotherapy may alleviate symptoms[31]. We, likewise, observed short-course (palliative) radiotherapy without surgery most often at older ages.

Strengths and limitations

This paper shows novel and recent data concerning nationwide treatment trends for patients with rectal cancer. It provides a comprehensive overview stratified for risk groups, enabling the evaluation of compliance with changing guidelines for these specific groups.

Limitations include the necessity of using an alternative risk group classification. However, the alternative classification showed comparable treatment trends in 2015-2021 to the original classification (Supplementary Figures 2-4), suggesting that it was a relatively accurate method of classification for investigating treatment patterns. In addition, it was impossible to adjust all analyses for comorbidities and performance status given their limited availability. Information on dosage and fractionation schemes were also unavailable, hampering the evaluation of potentially changing radiotherapy schemes.

Conclusions

This paper illustrates the changing landscape regarding radiotherapeutic treatment in the context of multimodal treatment for rectal cancer between 2008-2021 in the Netherlands, characterized in particular by the introduction of the national screening program for colorectal cancer and the new national guideline for neoadjuvant treatment published in 2014. In addition, the beginning paradigm shift towards organ preservation is revealed, which is expected to expand within the coming years.

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Supplementary Figure 1. Regions in the Netherlands

Trends in therapies for Patients diagnosed with early rectal cancer over years of diagnosis - N = 8,235
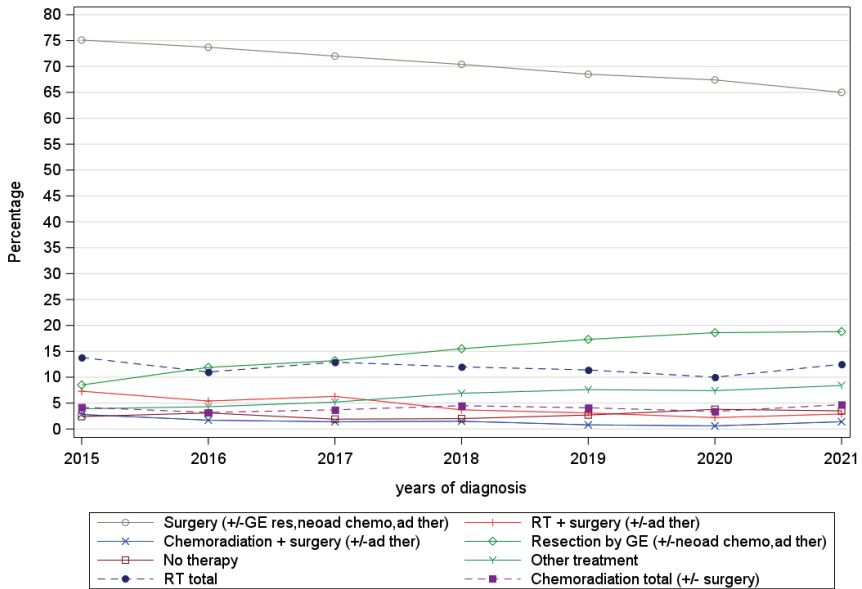
Supplementary Figure 2. Treatments for early rectal cancer using the original classification

Trends in therapies for Patients diagnosed with intermediate rectal cancer over years of diagnosis - N = 4,001
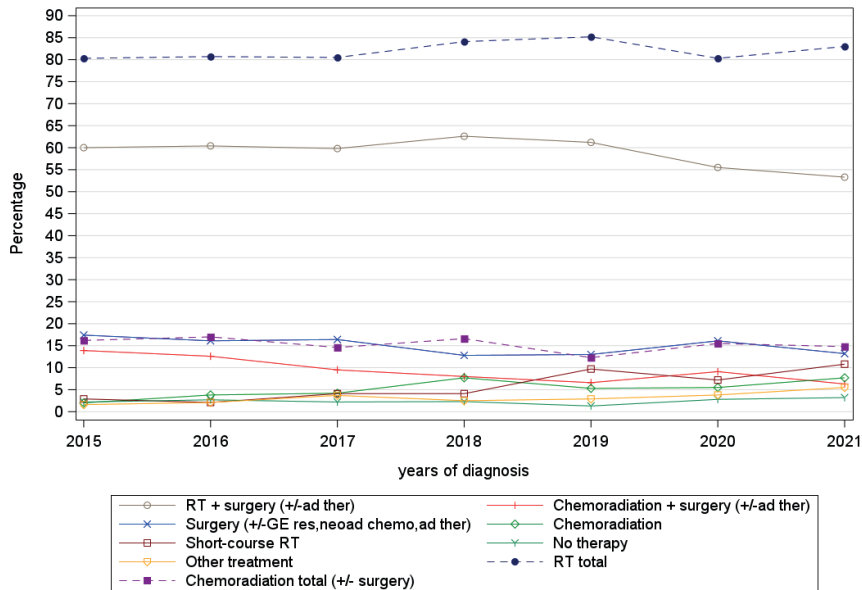
Supplementary Figure 3. Treatments for intermediate rectal cancer using the original classification
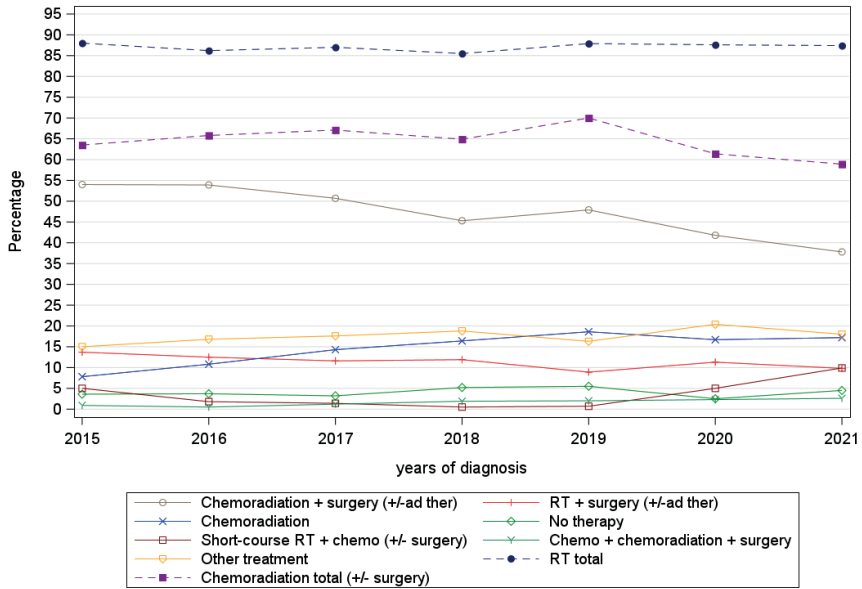
Supplementary Figure 4. Treatments for locally advanced rectal cancer using the original classification
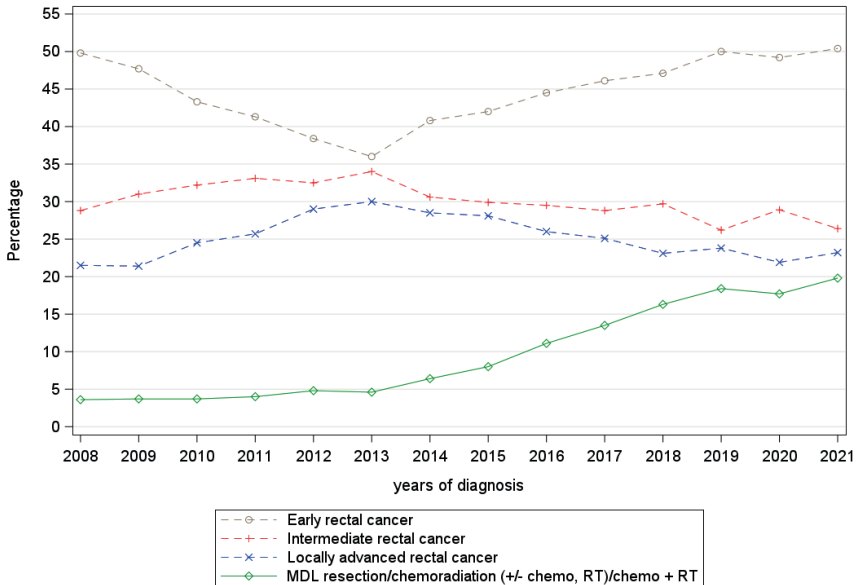
Supplementary Figure 5. Trends in disease stage, and use of gastroenterological resection and chemoradiation without surgery

A

Trends in therapies for Patients diagnosed with M0 rectal cancer over years of diagnosis - N = 25,210
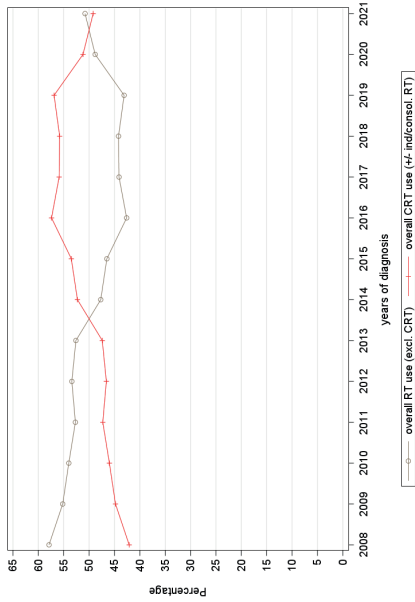
B

Trends in therapies for Patients in the North region diagnosed with M0 rectal cancer over years of diagnosis - N = 3,539

C
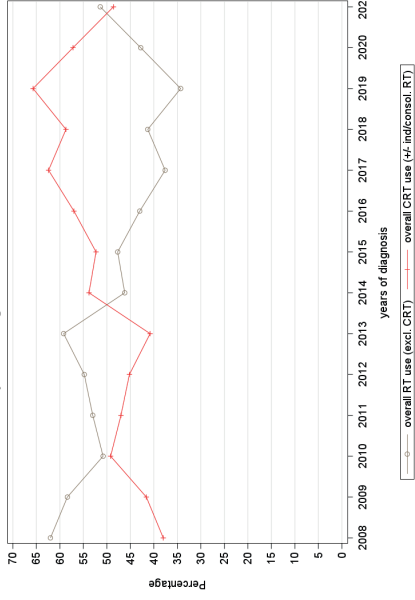
Trends in therapies for Patients in the East region diagnosed with M0 rectal cancer over years of diagnosis - N = 4,487
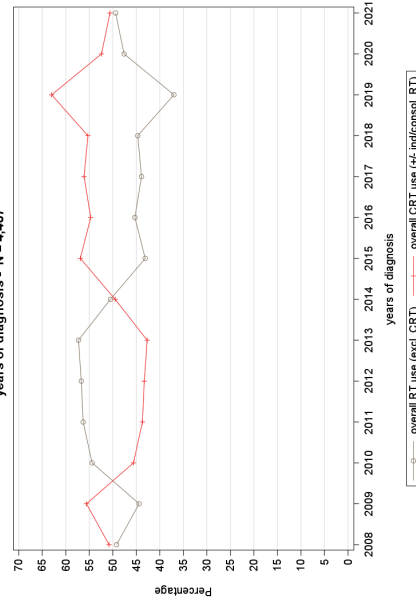
D

Trends in therapies for Patients in the South region diagnosed with M0 rectal cancer over years of diagnosis - N = 6,416
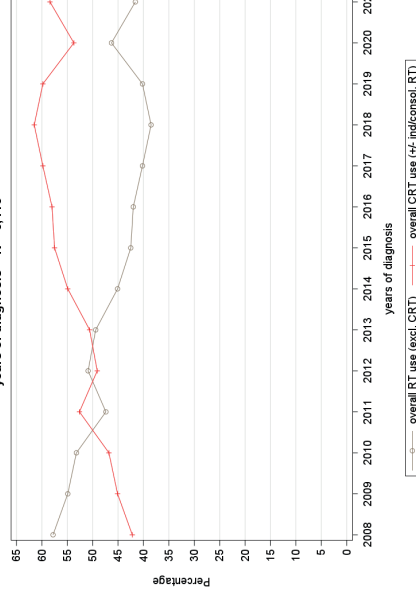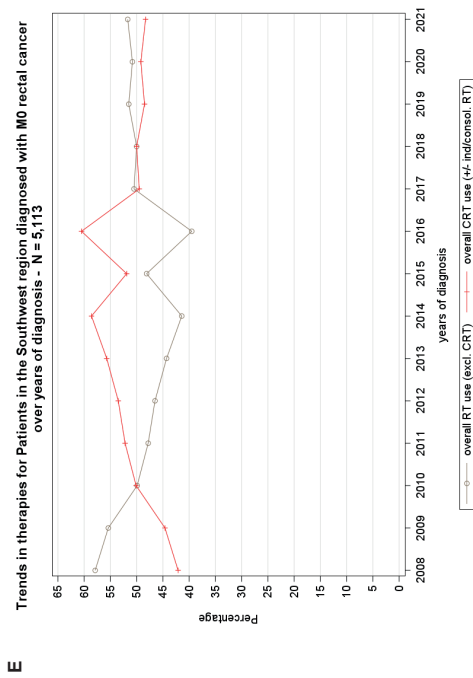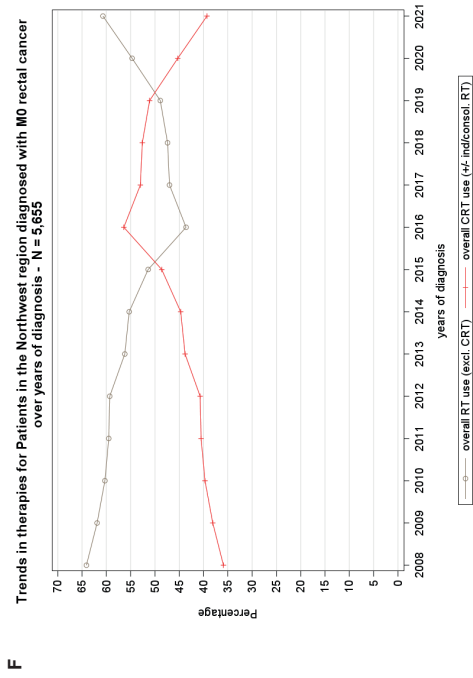
Supplementary Figure 6A-F. Overall use of radiotherapy versus chemoradiotherapy over time, total and stratified for region

A

Trends in therapies for Patients in the North region diagnosed with loc advanced rectal cancer over years of diagnosis - N = 1,346

B

Trends in therapies for Patients in the East region diagnosed with loc advanced rectal cancer over years of diagnosis - N = 1,964

C

Trends in therapies for Patients in the South region diagnosed with loc advanced rectal cancer over years of diagnosis - N = 2,481

D

Trends in therapies for Patients in the Southwest region diagnosed with loc advanced rectal cancer over years of diagnosis - N = 1,673

Supplementary Figure 7A-E. Treatments for locally advanced rectal cancer, stratified for region

Supplementary Table 1. Categorization of comorbidities

Categories used in the current study	Original Charlson Comorbidity Index categories
● Previous malignancy (M0/M+)	● Tumor without malignancy
	● Metastatic malignancy
	● Lymphoma
	● Leukemia
● Myocardial infarction	● Myocardial infarction
● Congestive heart failure	● Congestive heart failure
● Peripheral vascular disease	● Peripheral vascular disease
● Cerebrovascular disease / hemiplegia	● Cerebrovascular disease
	● Hemiplegia
● Chronic pulmonary disease	● Chronic pulmonary disease
● Diabetes Mellitus	● Diabetes Mellitus
	● Diabetes Mellitus with end organ damage
● Renal disease	● Moderate / severe renal disease
● Liver disease	● Mild liver disease
	● Moderate / severe liver disease
● Ulcer disease	● Ulcer disease
● Dementia	● Dementia
● Rheumatoid Arthritis	● Connective tissue disease
● HIV	● AIDS

Comorbidities which could not be included in the above categories were disregarded
Categories were not assigned weights

Supplementary Table 2. cT and cN in early, intermediate, locally advanced and unclassified M0 rectal cancer

	cT cN	n	%
Early (N = 16669)	cT1 cN0	2849	6,6
	cT1 cNX	583	1,3
	cT2 cN0	6411	14,8
	cT2 cNX	464	1,1
	cT3 cN0	5608	12,9
	cT3 cNX	754	1,7
Intermediate (N = 11291)	cT1 cN1	176	0,4
	cT2 cN1	1854	4,3
	cT3 cN0	1284	3,0
	cT3 cN1	7293	16,8
	cT3 cNX	170	0,4
	cTX cN1	514	1,2
Locally advanced (N = 9550)	cT1 cN2	19	0,0
	cT2 cN2	462	1,1
	cT3 cN2	5136	11,8
	cT4 cN0	1000	2,3
	cT4 cN1	1190	2,7
	cT4 cN2	1359	3,1
	cT4 cNX	272	0,6
	cTX cN2	112	0,3
Unclassified (N = 5877)	cTX cN0	3678	8,5
	cTX cNX	2199	5,1

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Supplementary Table 3. Adjusted odds ratios (OR) of receiving chemoradiation (CRT) without surgery versus CRT with surgery, for patients aged < 70 years diagnosed with locally advanced rectal cancer since 2014 in the Netherlands (N=2,801)

	Diagnosed since 2014	
	CRT without surgery, N = 456	
	CRT, N = 2,345	
	OR [A]	**(95%CI)**
Year of diagnosis (continuously)	**1.22**	**(1.16-1.27)**
Sex		
Men	Reference	
Women	0.88	(0.72-1.09)
Age at time of diagnosis		
< 50 years	Reference	
50-69 years	1.33	(0.99-1.78)
Region of residence		
North	Reference	
East	0.81	(0.54-1.21)
South	**0.58**	**(0.38-0.90)**
Southwest	**0.54**	**(0.34-0.84)**
Northwest	**0.57**	**(0.37-0.88)**
Comorbidities [B]		
No comorbidity in any CCI category	Reference	
Comorbidity in 1 CCI category	1.04	(0.63-1.69)
Comorbidity in ≥2 CCI categories	1.78	(0.94-3.37)
WHO performance status [C]		
Performance status 0	Reference	
Performance status 1	0.96	(0.73-1.25)
Performance status 2-4	1.40	(0.77-2.53)
Hospital of surgery		
Non-university	Reference	
University [D]	**2.00**	**(1.22-3.28)**
Volume in the hospital of surgery [E]		
Low volume of diagnoses	Reference	
Intermediate volume of diagnoses	**1.62**	**(1.04-2.51)**
High volume of diagnoses	1.56	(1.00-2.42)

Continued

OR: odds ratio, CRT: chemoradiation, 95%CI: 95%% confidence interval, CCI: Charlson Comorbidity Index; values in bold are statistically significant

A   A multilevel logistic regression models with both a random intercept and random effect was applied for number of comorbidities. The analyses on year of diagnosis, sex and region were not adjusted, as none of the variables fulfilled the criterium for inclusion in the adjustment sets. The analyses on age and performance status were adjusted for year of diagnosis. The analysis on number of comorbidities was adjusted for age. The analysis on type of hospital was adjusted for year of diagnosis, region and volume of diagnosis. The analysis on volume of diagnosis was adjusted for type of hospital. NB. number of comorbidities and performance status were not included in adjustment sets, considering their limited availability.

C   Comorbidities were assessed for 1,294 (46%) of the patients diagnosed since 2014.

D   WHO performance status was available for 1,877 (67%) of the patients diagnosed since 2014.

E   Including the single cancer specific hospital in the Netherlands.

F   The one third of hospitals with the lowest number of M0 rectal cancer diagnoses (average ≤22 p/year) were classified as low volume, the one third of hospitals with the highest number of M0 rectal cancer diagnoses (average ≥42 p/year) were classified as high volume, the other one third of hospitals were classified as intermediate volume.

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CHAPTER

8

GENERAL DISCUSSION

This thesis provides an overview of the nationwide trends and variations in the use of primary radiotherapy in non-metastatic non-small cell lung cancer (NSCLC) (chapter 2), small cell lung cancer (SCLC) (chapter 3), ductal carcinoma in situ of the breast (DCIS) (chapter 4), invasive breast cancer (chapter 5), prostate cancer (chapter 6) and rectal cancer (chapter 7). While the various chapters each describe results for one of the aforementioned types of tumors, this general discussion discusses results for multiple tumors in the broader context of developments that continuously change the eligibility of radiotherapy and therefore drive change in treatment patterns. Like in the introduction of this thesis, three types of developments with the potential of changing radiotherapy use over time will be addressed: *technical developments*, *novel insights in optimal treatment* and *organizational developments*.

Technical developments

Technical developments in radiotherapy encompass both advancements in the techniques of target localization, dose planning, and radiotherapy delivery. Developments in the techniques of diagnostic procedures or other possibly competing treatment modalities have potential of changing radiotherapy eligibility as well. In the years since 2008, which were investigated in our studies, multiple technological advancements were implemented and became more widespread.

One of these advancements is stereotactic body radiotherapy (SBRT), which was implemented as a treatment option in NSCLC in international treatment guidelines around 2010 [1-6]. We observed changing treatment patterns in NSCLC following this implementation. The use of radiotherapy in clinical stage I disease strongly increased, coinciding a substantial decrease in use of surgical resection. This suggests a shift from surgery to radiotherapy (chapter 2). Remarkably, surgery was the preferred treatment strategy in treatment guidelines for patients with stage I NSCLC, while SBRT was preferred as curative-intent treatment option in patients who were deemed inoperable or those not willing to accept the risks of surgery [7].

Another major technical development in radiotherapy in the Netherlands is the introduction of proton beam radiotherapy in 2018 [8]. While proton beam radiotherapy is indicated in the Netherlands for some groups of patients (e.g. children) [9], most other patients are selected using a model-based approach in which an up-front prediction of benefit by proton versus photon therapy should

justify referral for proton beam radiotherapy. This is for example the case in selected cases of breast and lung cancer [9,10]. Since 2018, the number of facilities providing proton beam radiotherapy in the Netherlands increased to three, and the number of patients considered for proton therapy as well as the number of patients referred for proton beam radiotherapy gradually increased [11]. Given this implementation phase, interpreting the effect of the introduction of proton beam radiotherapy on radiotherapy treatment patterns in the Netherlands is challenging. Hence, we did not evaluate the use of proton beam radiotherapy in our studies.

In treatment of invasive breast cancer with lymph node micrometastatic disease, we observed a treatment pattern that also may be explained by a technological development. It has been suggested that regional treatment can be de-escalated in case of sentinel node micrometastases [12]. However, the axillary coverage of today's whole breast irradiation is less than before as result of technical developments in conformal whole breast irradiation [13]. We observed decreasing yet frequent use of regional treatment (i.e. axillary lymph node dissection and/or regional radiotherapy), which may be explained by this technological advancement affecting axillary coverage and consequently the decision for regional treatment in case of micrometastatic nodal disease.

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In addition to these technical developments in radiotherapy, technical developments in diagnostic procedures or other treatment modalities also have the potential of changing radiotherapy use. Technological advancements in diagnostic procedures continuously improve the detection of metastases and the imaging of the primary tumor. As a result, disease staging improves and the phenomenon called "stage migration" occurs. Stage migration is characterized by improved survival in all stages because less patients with higher tumor burden are falsely included in lower disease stages and the higher stages include more patients with lower tumor burden than before, and because patients in each disease stage better suit the provided treatment than before [14]. Improved stage-stratified survival may add to the introduction of novel stage-specific treatment strategies aiming to de-intensify treatment in order to prevent adverse effects. To illustrate, technological advancements in imaging improved the staging of NSCLC, which contributed to improved stage-specific survival [15]. This may have added to the feasibility of using non-invasive SBRT in patients with stage I NSCLC who previously would have undergone surgery (chapter 2).

Prominent technical developments in a non-radiotherapy treatment modality can potentially also impact radiotherapy use. For example, robot-assistance

in radical prostatectomy, which became widespread in the Netherlands in the last two decades [16]. In many prostate cancer cases, prostatectomy and radiotherapy (primary external beam radiotherapy (EBRT) or brachy-monotherapy) are competing treatment options. As robot-assistance in performing prostatectomies aims to decrease the risk of surgical complications, its increased availability had the potential to change treatment decision in prostate cancer in favor of prostatectomies and at cost of the utilization of radiotherapy. However, our study on prostate cancer did not show evident signs of a shift from radiotherapy to prostatectomy in intermediate and high-risk prostate cancer cases (chapter 6). Instead, increased use of both radical prostatectomies and EBRT was noted over time.

Novel insights in optimal treatment

Technical advancements and studies providing novel insights in which groups of patients benefit from which (new) treatment, may change the perception of the treatment strategy considered optimal. This changed perception on optimal treatment is a driver for changing (radiotherapy) treatment patterns, which we likewise observed in our studies.

As SBRT was demonstrated feasible in early NSCLC and favorable survival outcomes were reported for surgery in cohorts and retrospective series on SCLC, both surgery and SBRT became considered treatment options in very early stages of SCLC [17-19]. We have observed that this changed perspective on treatment possibilities in SCLC caused a shift in treatment of stage I disease from chemoradiation to surgery and SBRT. In stage II-III SCLC, we have evaluated the use of twice-daily hypofractionated radiotherapy in the context of concurrent chemoradiation. Twice-daily compared to once-daily radiotherapy in concurrent chemoradiation seemed more effective in the late '90s Turrisi-trial [20]. Although this provided a novel insight in optimal treatment, concerns on the toxicity of twice-daily radiotherapy existed, as well as concerns regarding the relatively low dose administered in the once-daily arm of this trial [21,22]. We showed that the implementation of a twice-daily regimen was hampered until 2012 (chapter 3), and thereafter gained uptake – probably by increased confidence in the effectiveness and toxicity of a twice-daily regimen. The CONVERT-trial, first presented in 2015, investigated if once-daily radiotherapy with a biologically equivalent dosage was superior to twice-daily radiotherapy. This trial reaffirmed the twice-daily regimen's effectiveness

by not demonstrating superiority of once-daily radiotherapy and by showing comparable toxicity rates in once- and twice-daily radiotherapy [23].

In low-risk prostate cancer and DCIS, focus has been brought to de-intensification of treatment [24-28]. In low-risk prostate cancer, immediate treatment does more harm than it yields benefit. In low-risk DCIS, only a minority of cases will progress to invasive breast cancer [29-31]. Hence, in both types of tumors, an active surveillance strategy with optionally deferred treatment is nowadays considered optimal or at least appropriate instead of immediate treatment. We investigated the actual application of deferred treatment and indeed observed decreased use of primary active treatment (both regarding surgery and radiotherapy) in localized low-risk prostate cancer (chapter 6) and DCIS grade I-II (chapter 4). In DCIS grade I-II, we furthermore observed decreased use of radiotherapy following breast-conserving surgery and a shift from whole breast irradiation with boost to whole breast irradiation without boost and to partial breast irradiation.

In invasive breast cancer, efforts were also taken in identifying subgroups of patients with a favorable prognosis in whom treatment could be de-escalated. Consequently, subgroups of patients at low risk of local recurrences were identified in whom radiotherapy following breast-conserving surgery could be omitted [32-35]. Furthermore, partial breast irradiation or whole breast irradiation without a boost is increasingly accepted as optimal treatment in low-risk breast cancer, given the low absolute recurrence rate, the lack of survival benefit by boost irradiation and the impaired cosmetic outcomes following boost irradiation [36-45]. We investigated radiotherapy use following breast-conserving surgery in patients with invasive breast cancer and indeed observed decreased use of radiotherapy following surgery, as well as increased use of partial breast irradiation and a further omission of a boost in whole breast irradiation (chapter 5). Also, we observed a shift from axillary lymph node dissection to regional radiotherapy in patients with nodal involvement. The latter is nowadays considered a feasible treatment option for limited regional disease in breast cancer, considering that research showed that recurrence rates and overall survival did not differ for axillary lymph node dissection and axillary radiotherapy [46-48].

In rectal cancer, the rate of patients with a clinical complete response following neoadjuvant chemoradiation paved the way for an organ-preserving "watch-and-wait"-strategy [49]. We showed that this changed perspective on optimal treatment was well-adopted by clinical practice, as surgery following (chemo) radiation was increasingly omitted in intermediate and locally advanced rectal cancer (chapter 7).

Also in rectal cancer, neoadjuvant treatment was optimized by further specifying the subgroups of patients benefitting from neoadjuvant radiotherapy and neoadjuvant chemotherapy. In line with this specification, we observed decreased use of neoadjuvant (chemo)radiotherapy in early-stage rectal cancer and a shift from neoadjuvant chemoradiation to neoadjuvant radiotherapy in intermediate stage rectal cancer (chapter 7). In locally advanced rectal cancer, the above-mentioned organ-preserving "watch-and-wait"-strategy is nowadays considered an option given that a clinical complete response after neoadjuvant chemoradiation is achieved [49]. Also, intensification of neoadjuvant therapy in locally advanced disease is nowadays considered, at the aim of increasing the likelihood of a clinical complete response [50-53]. In addition to the observed increased omission of surgery following chemoradiation in rectal cancer, we observed increased use of chemotherapy preceding chemoradiotherapy or radiotherapy. This potentially reflects the intensification of neoadjuvant therapy at the aim of increasing the likelihood of a complete response and omit surgery.

Organizational developments

In order to increase the quality and outcomes of oncological care and to (further) uniform oncological care throughout the country, various (re) organizational developments have taken place in the years since 2008. These developments are a third driver for changing radiotherapy treatment patterns in the Netherlands, as we observed in our studies.

At the aim of diagnosing and removing colorectal tumors at a pre-malignant stage, which prevents colorectal cancer, a nationwide colorectal cancer screening program has been implemented in the Netherlands since 2014 [54]. We showed that the screening program came with an increase of endoscopic resections of early rectal cancer, an increased number of diagnosed prevalent cases, and – a few years after implementation of the screening program – a decreased overall number of rectal cancer diagnoses because of lesions being removed at a premalignant stage. Furthermore, the proportion of rectal cancer diagnoses being early stage increased by the introduction of the screening program (chapter 7). As stated before, we showed that early rectal cancer is no longer commonly treated with neoadjuvant (chemo)radiotherapy. Hence, the implementation of the screening program substantially decreased the numbers of patients with rectal cancer being irradiated.

Since 2008, the number of radiotherapy facilities performing brachytherapy for early-stage prostate cancer declined. For EBRT, an opposed trend of opening additional facilities has taken place. This reduced the travel time and potentially improved the access for EBRT, especially in the more rural areas (Figure 1). In stage I-II NSCLC and intermediate and high-risk prostate cancer, we have shown that a longer travel time for radiotherapy was associated with less radiotherapy instead of surgery (chapters 2 and 6). In stage II-III SCLC, we found increased travel time for radiotherapy to be associated with less twice-daily radiotherapy in the context of concurrent chemoradiation (chapter 3). This association can be explained by twice-daily compared to once-daily radiotherapy requiring extra travel time for the patient on a single day, as staying at the radiotherapy facility in the time between the two fractions on the day is often not an option. Despite our findings on treatment variation in relation to radiotherapy travel time, it is difficult to evaluate the effects of opening additional radiotherapy facilities on the use of radiotherapy. The reason for this is that the additional facilities were opened gradually over time, causing overlap with other important developments impacting choice for EBRT simultaneously happening – for example the introduction of SBRT in NSCLC treatment or the implementation of hypofractionation (and thus decreased overall travel time for radiotherapy) in the treatment of prostate cancer.
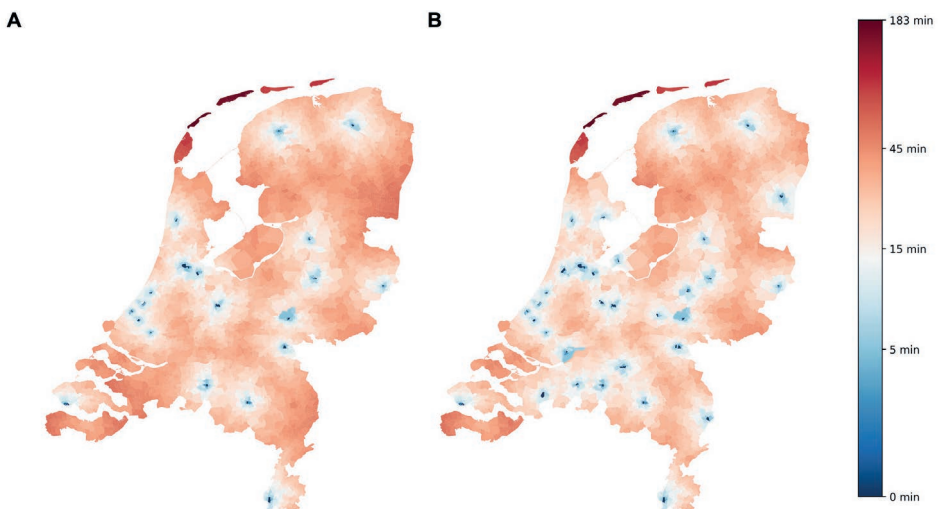

Figure 1. Travel time for external beam radiotherapy in the Netherlands in 2008 (A) versus 2023 (B)

In the last decades, the collaboration between hospitals within multidisciplinary team consultation, regional oncological networks and national professional associations increased [55-58]. All these collaborations promote treatment decisions which go beyond the expertise available in single hospitals. In our studies, however, we found regional treatment variations (chapters 2, 3, 5, 6, and 7) which possibly reflect differences in local treatment protocols. Also, treatment variations were found for characteristics of the hospitals which diagnose and where is decided upon treatment. To illustrate, treatment patterns are different in university versus non-university hospitals (chapters 2, 3, 4, 6, and 7), which may reflect earlier implementation of technical advancements or earlier adoption of novel treatment strategies. Treatment variation related to the available expertise in the diagnosing hospital was most evident in our study on prostate cancer (chapter 6). In intermediate and high-risk prostate cancer, patients diagnosed in hospitals with a radiotherapy department were more likely to receive EBRT instead of prostatectomy than those diagnosed in a hospital without a radiotherapy department. On the other hand, patients diagnosed in a hospital performing prostatectomy were less likely to receive EBRT instead of prostatectomy than those diagnosed in a hospital not performing prostatectomy. For low-risk prostate cancer, no association was found between the presence of a radiotherapy department in the diagnosing hospital and the use of EBRT instead of no active treatment. In many of the intermediate and high-risk prostate cancer cases, radiotherapy and prostatectomy are competing treatment options, while in low-risk prostate cancer no active treatment is preferred over EBRT or another immediate treatment. This implies that the available expertise in the hospital of diagnosis contributes to the treatment decision only in case of comparable treatment options.

What can we learn from treatment patterns?

In this thesis, we provide an overview of the nationwide trends and variations in the use of primary radiotherapy in the context of other treatment modalities. We observed changing use of radiotherapy and other treatment modalities, which partly reflects changes in the eligibility of the respective treatment strategy; sometimes (rapidly) following treatment guideline adaptions and sometimes preceding guideline adaptions. Also, we found treatment variations between patients, reflecting differences in frailty as well as risk of a poor outcome, and probably reflecting differences in patient preferences. We further found

differences in treatment strategy across the country and differences related to hospital-characteristics, which may reflect different treatment protocols or the available in house-expertise. In all our studies, our goal was to signal and to make clinicians aware of the nationwide treatment patterns and variations. Clinicians (but also policy makers) are helped by these insights when evaluating the implementation of technical advancements and new treatment approaches, and when assessing the consequences of organizational changes. Using our insights, they can improve treatment decisions if the observed treatment trends and variations are not desired, either by themselves or by finding agreement with each other within their hospital, or at a regional or national level.

Optimal treatment is based on the patients' preferences, treatment effectiveness, and contextual factors, such as comorbidities related to treatment tolerance and expected outcomes. Furthermore, treatment decisions should go beyond the expertise available in the single hospitals. Even though we lack information on the considerations in individual treatment decisions in the studies in this thesis, our population-level insights revealed potential opportunities for improving treatment decision. To illustrate, the found variation across the country in use of radiotherapy versus surgery in stage I-II NSCLC may justify discussions aiming to achieve nationwide agreement on the use of SBRT in early-stage NSCLC. Current treatment guidelines encompass SBRT as treatment option for stage I NSCLC in inoperable patients, those at high risk of surgical complications and those not willing to accept the risks of surgery. However, treatment guidelines still prefer surgery in those willing to accept the procedure-related risks, given the limited evidence directly comparing SBRT and surgery [1-6,59]. Trials are currently ongoing (NCT-02468024 and NCT-02984761) to prospectively compare these treatment strategies. Nevertheless, we observed a shift from surgery to radiotherapy in our study, resulting in radiotherapy becoming the predominant treatment strategy in stage I NSCLC. From our study, it remains uncertain whether this is caused by an increasing number of patients not willing to accept the risk of surgery (and thus preferring SBRT) – which was the reason of failing recruitment in the SABRTooth-trial (NCT-02629458) intended to compare SBRT with surgery [60]– or by increased believe of physicians in SBRT as valid alternative for surgery in operable patients with early stage NCSLC. In case of the latter, it is up to the clinicians to counter the discrepancy between guideline and practice by (providing the evidence

for) including SBRT in the guidelines as an equivalent treatment alternative to surgery in (operable) patients with stage I NSCLC. Other (not exhaustive) examples of potentially actionable insights that were provided by studies in this thesis regard the decreasing use of primary brachy-monotherapy in low and intermediate-risk prostate cancer, the increased omission of breast conserving surgery and radiotherapy in low-risk patients with invasive breast cancer and DCIS, the variation across the country regarding omission of surgery after chemoradiation in rectal cancer, and the variation in treatment provided to patients with intermediate and high-risk prostate cancer depending on the expertise available in the diagnosing hospital.

Future use of radiotherapy

With the studies in this thesis, we have aimed to contribute to the ongoing quest of optimizing oncological care. Because of this continuous optimization, future decisions on radiotherapy use likely differ from the treatment decisions in the past. This matter makes it challenging to forecast the capacity of radiotherapy needed in the future. Nevertheless, forecasting the future need for radiotherapy is essential in the context of healthcare organization, to ensure timely access to radiotherapy in the future while preventing overcapacity.

Methodological framework

We set up a methodological framework to forecast *the future number of patients receiving primary radiotherapy in non-metastatic stages of cancer*. The future number of patients receiving radiotherapy is determined by the future number of cancer diagnoses and the future indications/decisions on treating patients by radiotherapy. Our methodological framework firstly forecasts the incidence of cancer up to 13 years and secondly predicts radiotherapy use in this future population diagnosed with cancer.

In the framework, demographic forecasts of Statistics Netherlands are used, as well as retrospective data from the population-based Netherlands Cancer Registry. Data on radiotherapy in metastatic disease, non-primary radiotherapy, dosage, and fractionation schemes are only limited available in the Netherlands Cancer Registry and could not be forecasted in the model. In order to obtain a complete estimate of the *total use of radiotherapy in the future* as well as an estimate of the *radiotherapy capacity needed in the future,*

information on radiotherapy in metastatic disease, non-primary radiotherapy, and fractionation schemes is essential. However, this goes beyond the scope of the framework.

An overview of the methodological framework can be found in Figure 2. Below, more information is provided on the forecast of cancer incidence, and the prediction of radiotherapy use in the future population diagnosed with cancer.
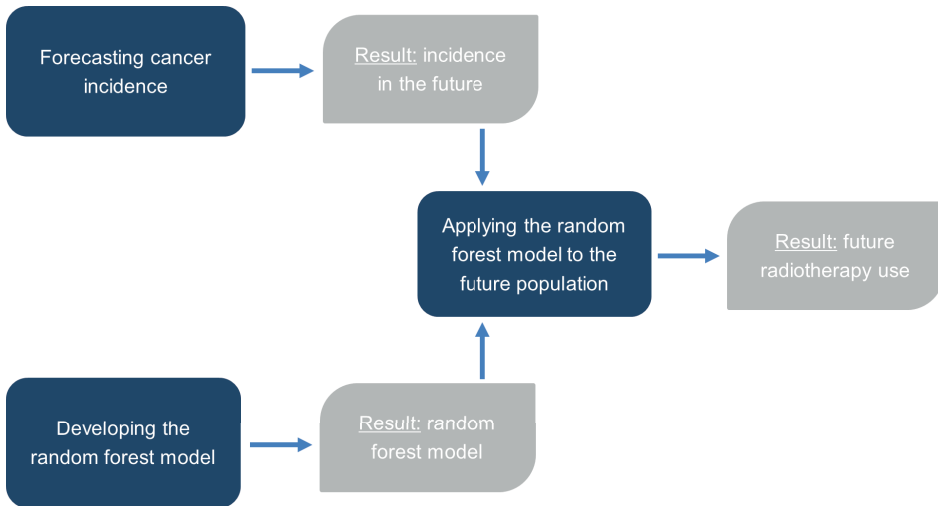
Figure 2. Overview of the methodological framework

Forecasting cancer incidence

The ability of forecasting future cancer incidences using retrospective data from population-based registries as the NCR was previously demonstrated [61-65]. In our framework, we apply a Poisson generalized linear age-period-cohort (APC) model for the forecast of cancer incidence. The benefit of an APC model is that it estimates an age-response curve and a birth cohort-response curve, which allows the association between age and cancer incidence to change over time [66]. Previously, the 'Nordpred' age-period-cohort model, developed at the Norwegian Cancer Registry, was used for forecasting cancer incidences in among others the Netherlands, Norway, Denmark, Sweden, and Finland [61,62]. However, the Nordpred-model imposes arbitrary model specifications [67]. To illustrate, the age groups, periods and birth cohorts selected as reference in the modelling are pre-defined and the input data and forecasted incidences are clustered in 5-year periods by 5-year age groups. Instead, we

chose to define the model specifications ourselves, as well as the number of past years to include as input. Ideally this is done by validation, in which the cancer incidences in the most recently observed years are forecasted using various age-period-cohort models with different specifications and a varying number of years before the forecasted period as input. The model which best forecasts the cancer incidence in the most recently observed years using retrospective data (the model with the specifications and number of input years best performing based on the mean absolute error) is then selected and used for forecasting the future cancer incidence. Furthermore, we chose not to cluster the incidences of cancer in multiple years, neither in the input data nor in the forecast.

In the context of the methodological framework, the forecast of cancers is preferably stratified into specific types of tumors and tumor-specific risk groups which are known to be associated with radiotherapy use. This accommodates for potential changes over time in the distributions of tumor types and risk groups, which would cause a misestimation of future radiotherapy use in case of no stratification.

Predicting radiotherapy use

In addition to tumor types and risk groups, patient-, hospital- and further disease-related factors are associated with the use of radiotherapy – as we demonstrated in our studies. The use of radiotherapy in the future population can be predicted using these patient-, hospital- and disease-related factors in a random forest model. A random forest model creates many decision trees, with each tree having randomly selected variables from the input set at its decision nodes. Also, random forest models use varying thresholds in categorizing variables, which allows for better predicting the outcome in case of non-linear response curves and deepens out potential interaction with subsequent nodes. To predict an outcome – in our case the use of radiotherapy – random samples with replacement are drawn from the data and applied in the decision trees [68]. Due to these features, a random forest model is able to perform many uncorrelated predictions, which combined provide a robust prediction that is less dependent on the training data than traditional logistic regression analyses [69]. In our framework, a random forest model is developed using retrospective data of 5 recent years and applied to the forecasted future population diagnosed with cancer, to predict radiotherapy use in this future

population. Ideally, a separate random forest model is applied for each tumor type, as relevant factors may differ for the various types of tumors.

Demonstration of the framework

We demonstrated the framework by predicting the overall radiotherapy use up to 2032 for all types of non-metastatic cancer, excluding skin cancers and cancers with less than 5% of patients being irradiated. In addition, we predicted the future primary radiotherapy use in non-metastatic stages of five types of tumors frequently seen at radiotherapy facilities: NSCLC, DCIS, invasive breast cancer, prostate cancer, and rectal cancer. For DCIS and invasive breast cancer, radiotherapy use for not-first primary breast tumors were also predicted, considering the relatively frequent occurrence of not-first primary tumors in the breast. For the other tumor types, only the first tumor in the respective organ was included in the prediction. Radiotherapy use in SCLC was not predicted, considering the low number of patients with stage I-III disease, which would result in highly uncertain predictions. For NSCLC, the model specifications and number of input years were decided on by the proposed validation approach. This validation was hampered in the predictions on the other tumor types, either by limited retrospective data being stratified for the applicable tumor-specific risk groups, or by known changes in incidence in the retrospective data which therefore cannot be used for validation. For all of our predictions, we used input data until 2019 in order to exclude the data from the COVID19-pandemic. To deal with the challenge of future decisions on radiotherapy use likely being different from the treatment decisions in the past, we decided to apply two types of predictions for all non-metastatic cancers and for each tumor type:

1)   We predicted future radiotherapy use by assuming that the retrospective data (including associations of patient-, hospital-, and disease-related factors with radiotherapy use) are representative for the future. We assumed similar distributions of variables in the future population compared to the current population; only the incidence would change over time, as well as the age-distribution in the patient population based on demographic forecasts.

2)   We adjusted the previous prediction by applying a likely or possible scenario which potentially impacts the future use of radiotherapy. For these

scenarios, we consulted with clinical experts to discuss the focus and design of the scenario. Some of the scenarios assumed changed distributions of variables (e.g. the scenario on recently opened/closed facilities affecting travel time), while others assume a change in the future incidence (e.g. the scenario on lung cancer screening affecting stage-specific incidences).

Predicted radiotherapy use up to 2032

All non-metastatic cancers

The future number of non-metastatic cancer diagnoses (excluding the previously mentioned types) is expected to increase from 57,517 in 2019 to 72,902 in 2032 (Figure 3A), with 33,680 patients receiving primary radiotherapy in 2032 (Figure 3B). In the retrospective data used as input, the radiotherapy facilities that have been opened Apeldoorn in 2020 and Utrecht in 2022 were not present, while the radiotherapy facility in Boxmeer – which closed in 2021 – was present. As the opening and closure of these facilities impacted the travel time for radiotherapy in the respective regions, we included the facilities in Utrecht and Apeldoorn and excluded the facility in Boxmeer in an adjusted prediction. Nevertheless, the predicted overall radiotherapy use remained the same in this adjusted scenario (Figure 3C).

NSCLC

For both clinical stage I and II NSCLC, increasing numbers of diagnoses are forecasted – up to 4,103 (Figure 4A) and 3,074 (Figure 5A) in 2032, respectively. Two thousand seventy-seven patients with stage I (Figure 4B) and 1,122 patients with stage II NSCLC (Figure 5B) are predicted to receive radiotherapy in 2032. In clinical stage III NSCLC, a decreasing incidence towards 1,984 patients in 2032 is predicted (Figure 6A), with 1,093 patients being irradiated in 2032 (Figure 6B). As scenario, we calculated the radiotherapy use in case a nationwide lung cancer screening program has been implemented, resulting in a shift towards earlier stages. For this scenario, we applied the same criteria as the currently ongoing "4-in-the-lung-run-trial" for defining eligible people [70]. The resulting numbers of patients with clinical stage I, II, and III NSCLC receiving radiotherapy in 2032 are 2,457 (Figure 4C), 1,117 (Figure 5C) and 1,017 (Figure 6C), respectively.

Overall (non-metastatic)

Skin cancers and cancers which are irradiated in <5% of cases were excluded

A.

Annual number of diagnoses

2019	57517
2020	58866
2021	60043
2022	61250
2023	62496
2024	63766
2025	65012
2026	66242
2027	67449
2028	68621
2029	69752
2030	70851
2031	71906
2032	72902

B. When assuming that the historical data are representative for the future

Radiotherapy use

2019	27394
2020	27991
2021	28515
2022	29031
2023	29553
2024	30069
2025	30574
2026	31064
2027	31503
2028	31949
2029	32395
2030	32839
2031	33273
2032	33680

C. When applying the scenario

Radiotherapy use

2019	27394
2020	27991
2021	28515
2022	29031
2023	29553
2024	30069
2025	30574
2026	31064
2027	31503
2028	31949
2029	32395
2030	32839
2031	33273
2032	33680

Figure 3. [A] Forecasted annual number of non-metastatic cancer diagnoses, [B] predicted annual number of irradiated patients in future years – assuming the retrospective data being representative, and [C] predicted annual number of irradiated patients in future years in the scenario with the current available radiotherapy facilities

Clinical stage I non-small cell lung cancer

Figure 4. [A] Forecasted annual number of clinical stage I non-small cell lung cancer diagnoses, [B] predicted annual number of irradiated patients in future years – assuming the retrospective data being representative, and [C] predicted annual number of irradiated patients in future years in the scenario of a lung cancer screening program

Clinical stage II non-small cell lung cancer
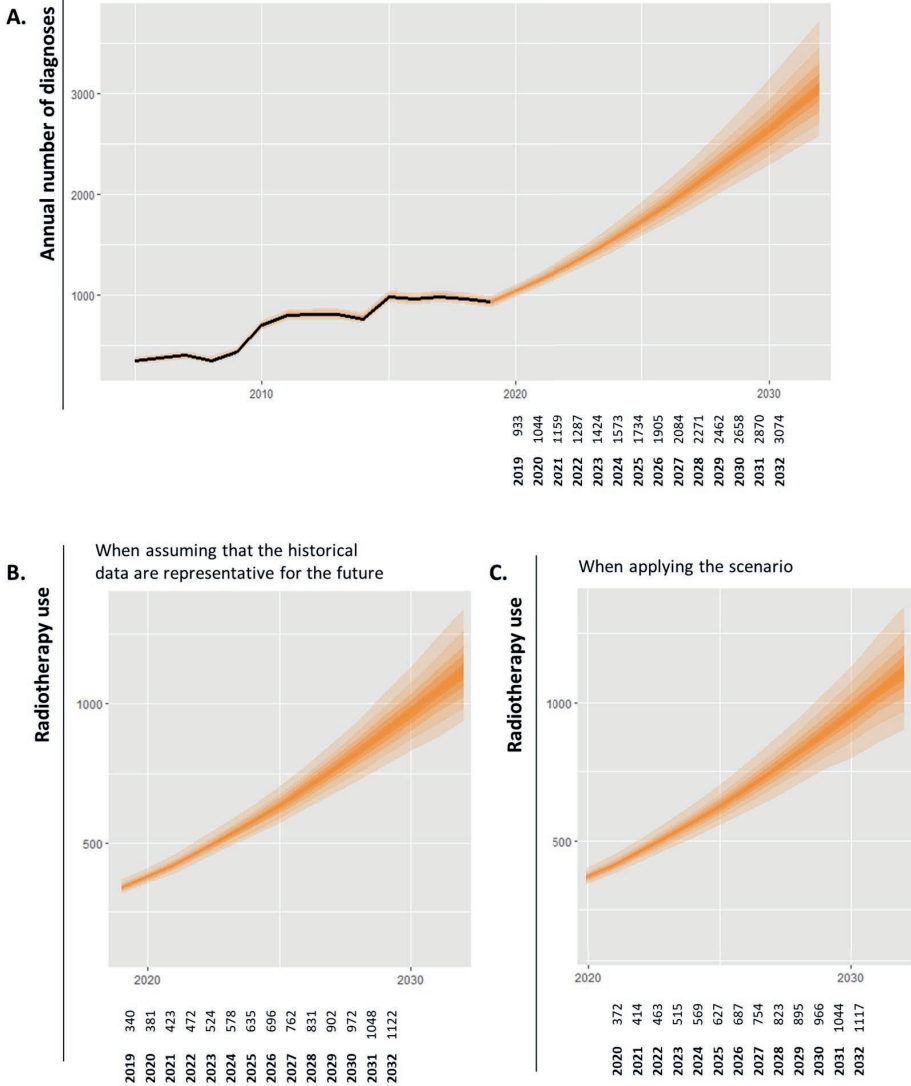
Figure 5. [A] Forecasted annual number of clinical stage II non-small cell lung cancer diagnoses, [B] predicted annual number of irradiated patients in future years – assuming the retrospective data being representative, and [C] predicted annual number of irradiated patients in future years in the scenario of a lung cancer screening program

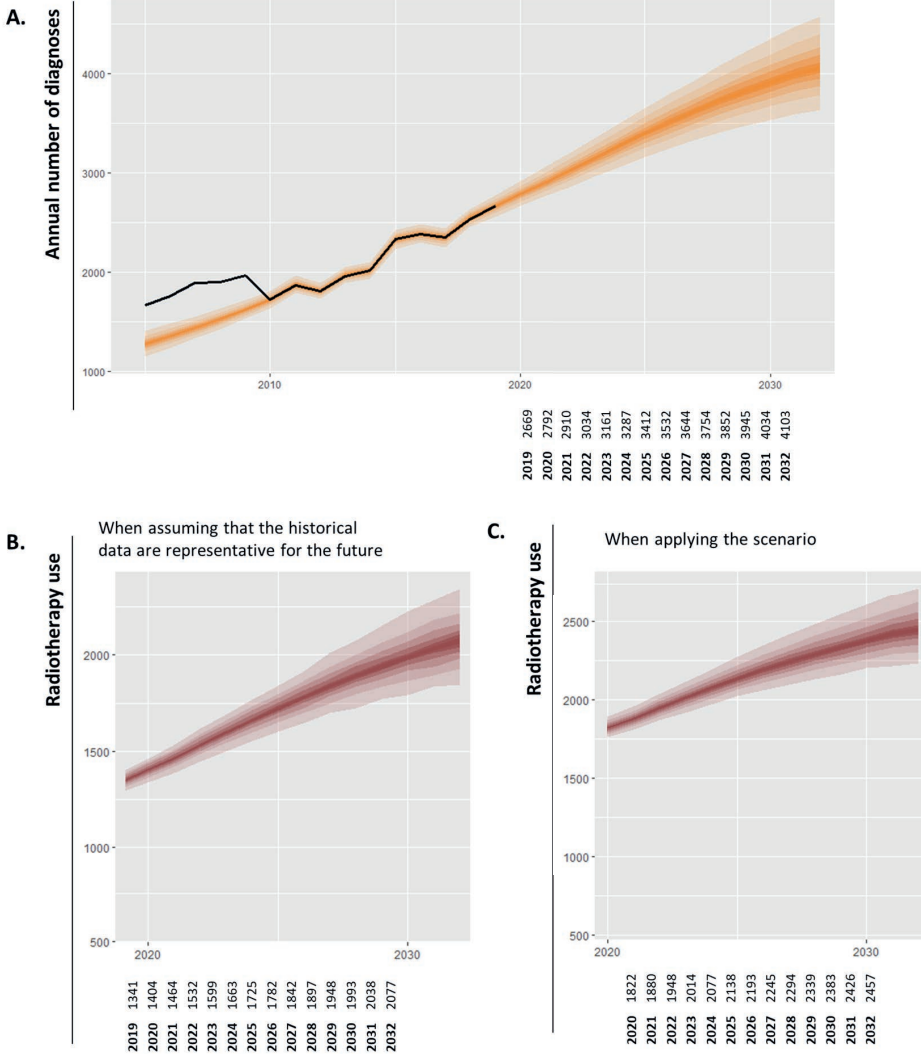**Clinical stage III non-small cell lung cancer**
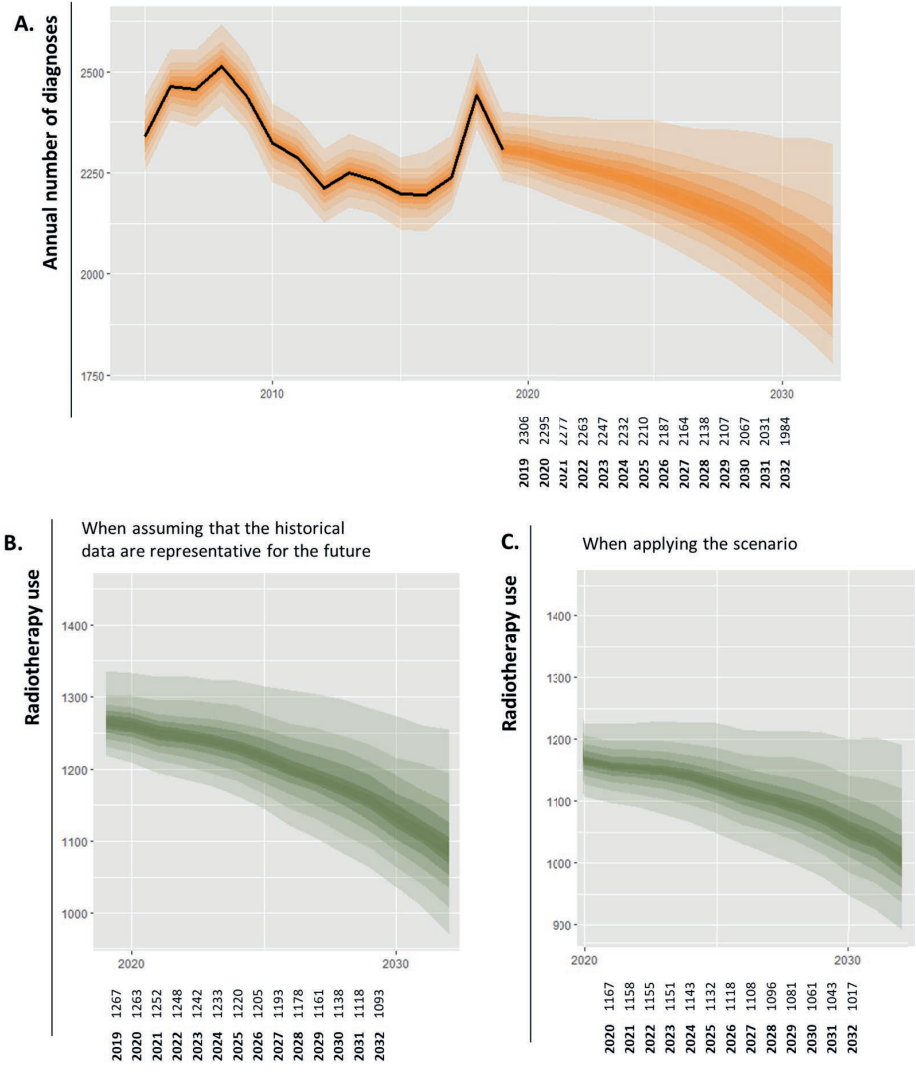
Figure 6. [A] Forecasted annual number of clinical stage III non-small cell lung cancer diagnoses, [B] predicted annual number of irradiated patients in future years – assuming the retrospective data being representative, and [C] predicted annual number of irradiated patients in future years in the scenario of a lung cancer screening program

DCIS

Increasing numbers of DCIS diagnoses are forecasted – up to 1,904 for DCIS grade I-II in 2032 being the first tumor in the breast (Figure 7A), 1,056 for DCIS grade III being the first tumor in the breast (Figure 8A), 441 for DCIS grade I-II not being the first tumor in the breast (Figure 9A), and 186 for DCIS grade III

not being the first tumor in the breast (Figure 10A). Of these women, 858, 609, 114, and 72 are predicted to receive radiotherapy in 2032 (Figure 7B, 8B, 9B, 10B, respectively). Considering the treatment de-escalation that we observed in DCIS grade I-II in our study on DCIS, we also calculated the future use of radiotherapy by applying a scenario of continued omission of radiotherapy in women aged ≥45 with DCIS grade I-II being the first tumor in the breast. In this scenario, the number of women receiving radiotherapy in 2032 decreased to 337 (Figure 7C).

Invasive breast cancer

The future number of women diagnosed with non-metastatic invasive breast cancer being the first tumor in the breast is expected to rise to 15,345 in 2032 (Figure 11A). For non-metastatic invasive breast cancer not being the first tumor in the breast, the number is expected to rise to 2,370 in 2032 (Figure 12A). The use of radiotherapy in 2032 is predicted to be 10,746 in women diagnosed with breast cancer being the first tumor in the breast (Figure 11B) and 1,009 in women diagnosed with breast cancer not being the first tumor (Figure 12B). When applying a scenario of continued omission of radiotherapy in first grade I-II tumors in the breast in older women aged ≥65, the number of women diagnosed with non-metastatic invasive breast cancer receiving radiotherapy in 2032 decreased to 9,116 (Figure 11C).

Prostate cancer

Increasing numbers of prostate cancer diagnoses are forecasted for localized low-risk and intermediate-risk disease, and locally advanced disease – up to 2,317 (Figure 13A), 4,711 (Figure 14A) and 4,065 in 2032 (Figure 16A), respectively. For localized high-risk disease, a decrease to 1,169 patients in 2032 is forecasted (Figure 15A).The numbers of patients predicted to receive EBRT and brachytherapy in 2032 were 128 and 140, respectively, in localized low-risk disease (Figure 13B-C), 1,174 and 532, respectively, in localized intermediate-risk disease (Figure 14B-C), 434 and 18, respectively, in localized high-risk disease (Figure 15B-C), and 2,042 and 68, respectively, in locally advanced disease (Figure 16B-C). Given the changing treatment decision in prostate cancer in recent years, we applied a scenario of continued decreasing brachytherapy use in all risk groups, increasing use of active surveillance in low-risk prostate cancer and decreasing use of prostatectomy in intermediate-risk prostate cancer. In this scenario, patients received EBRT instead of brachy-monotherapy and prostatectomy. The resulting numbers of patients receiving EBRT and brachytherapy in 2032 are 90 and 58,

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respectively, in localized low-risk disease (Figure 13D-E), 1,916 and 160, respectively, in localized intermediate-risk disease (Figure 14D-E), 434 and 5, respectively, in localized high-risk disease (Figure 15D-E), and 2,042 and 21, respectively, in locally advanced disease (Figure 16D-E).

Figure 7. [A] Forecasted annual number of diagnoses of DCIS grade I-II – being the first tumor in the breast, [B] predicted annual number of irradiated patients in future years – assuming the retrospective data being representative, and [C] predicted annual number of irradiated patients in future years in the scenario of continued treatment de-escalation

DCIS grade III

Based on the Bloom Richardson tumor grading

A.

2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
858	883	900	916	928	942	955	970	985	999	1012	1028	1042	1056

B. When assuming that the historical data are representative for the future

2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
498	512	523	532	539	547	554	563	571	579	586	594	602	609

Figure 8. [A] Forecasted annual number of diagnoses of DCIS grade III – being the first tumor in the breast, and [B] predicted annual number of irradiated patients in future years – assuming the retrospective data being representative

DCIS grade I-II (not being the first tumor in the breast)

Based on the Bloom Richardson tumor grading

A.

2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
196	208	223	238	253	269	286	305	324	345	368	394	418	441

B. When assuming that the historical data are representative for the future

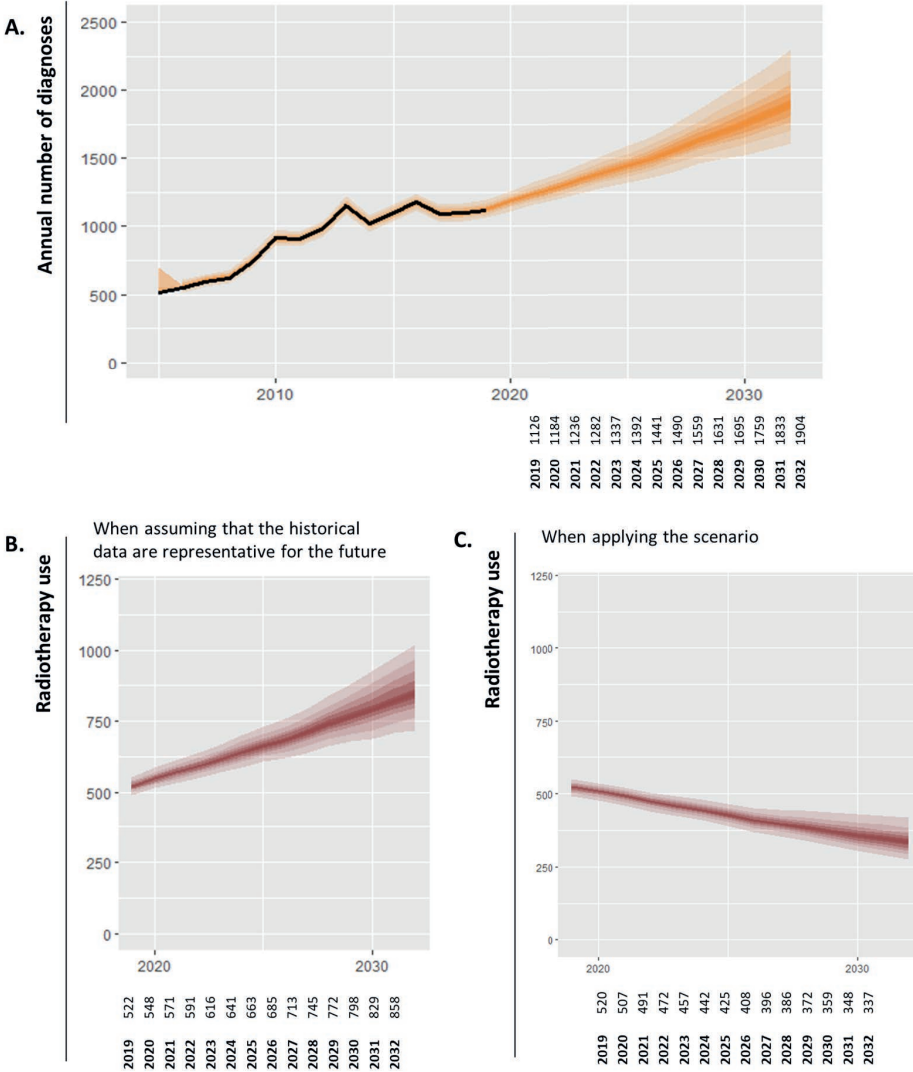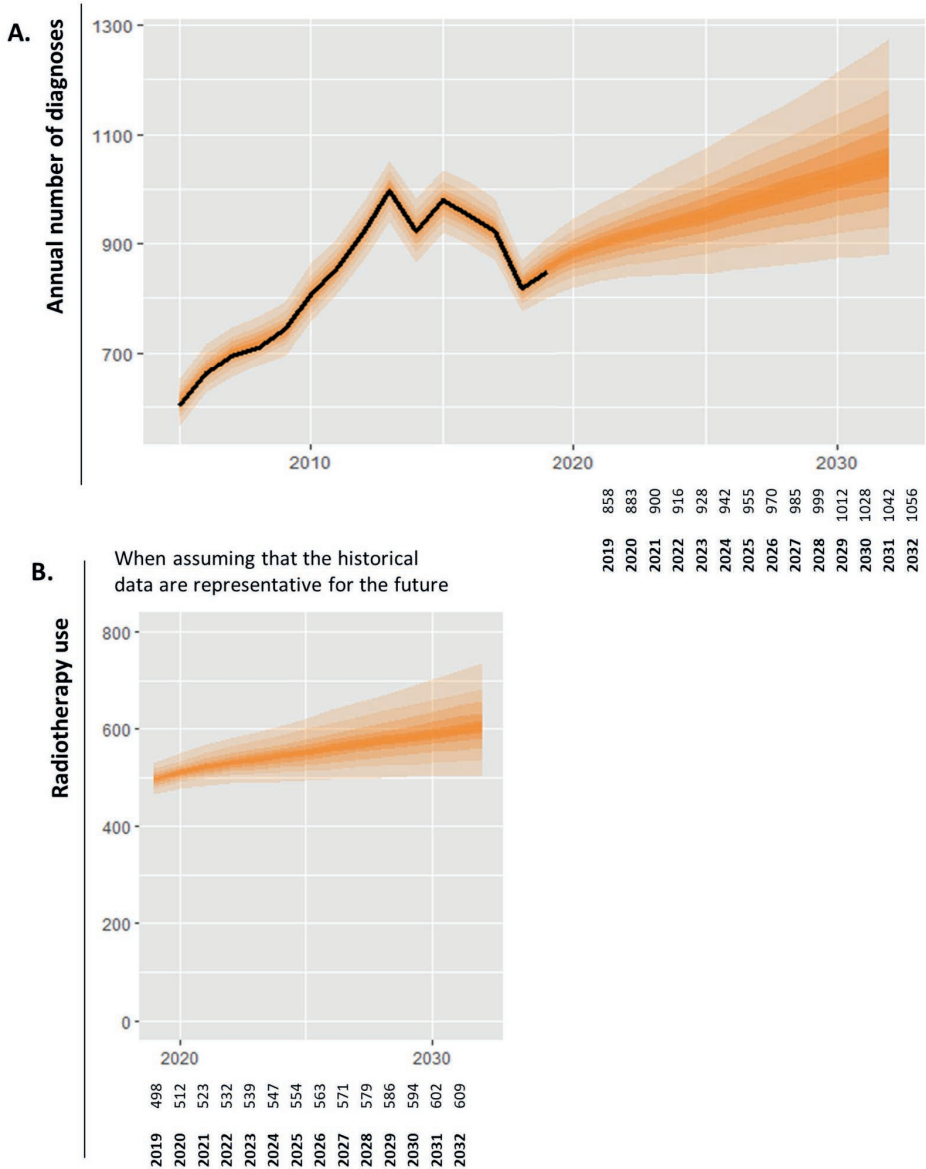| 2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
53	57	60	64	68	72	76	81	85	90	96	103	109	114

Figure 9. [A] Forecasted annual number of diagnoses of DCIS grade I-II – not being the first tumor in the breast, and [B] predicted annual number of irradiated patients in future years – assuming the retrospective data being representative

DCIS grade III (not being the first tumors in the breast)

Based on the Bloom Richardson tumor grading

A.

126	129	135	138	143	148	152	156	162	165	170	175	179	186
2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032

B.

When assuming that the historical data are representative for the future

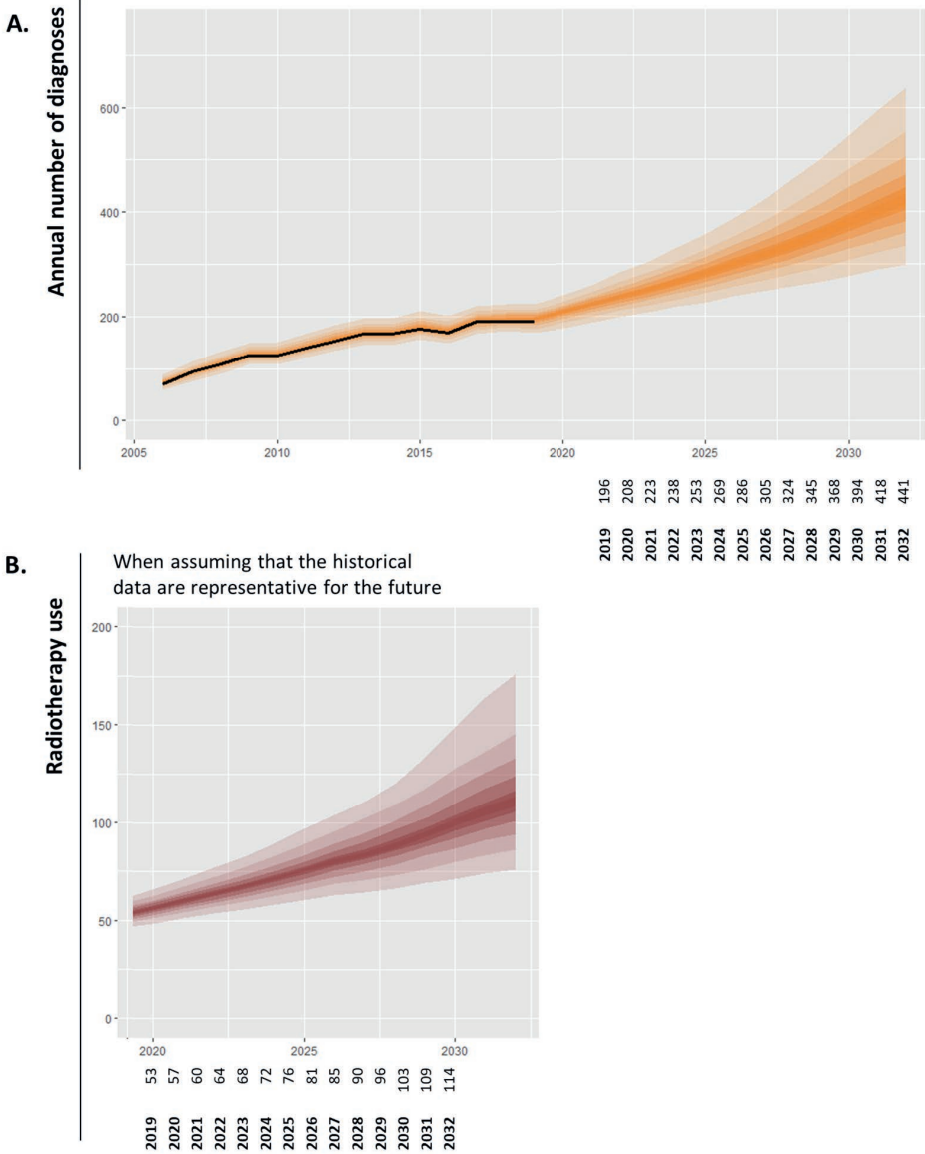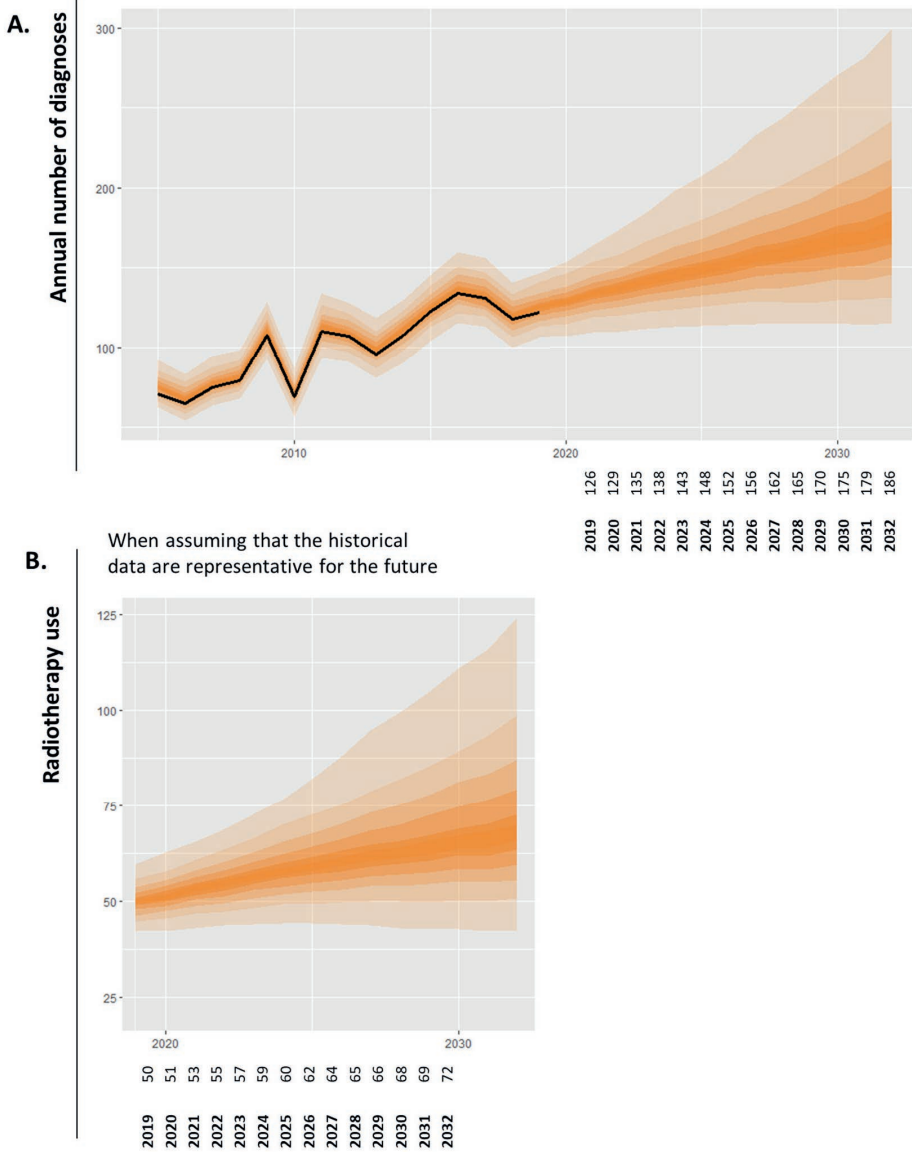|													
50	51	53	55	57	59	60	62	64	65	66	68	69	72
2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032

Figure 10. [A] Forecasted annual number of diagnoses of DCIS grade III – not being the first tumor in the breast, and [B] predicted annualnumber of irradiated patients in future years – assuming the retrospective data being representative

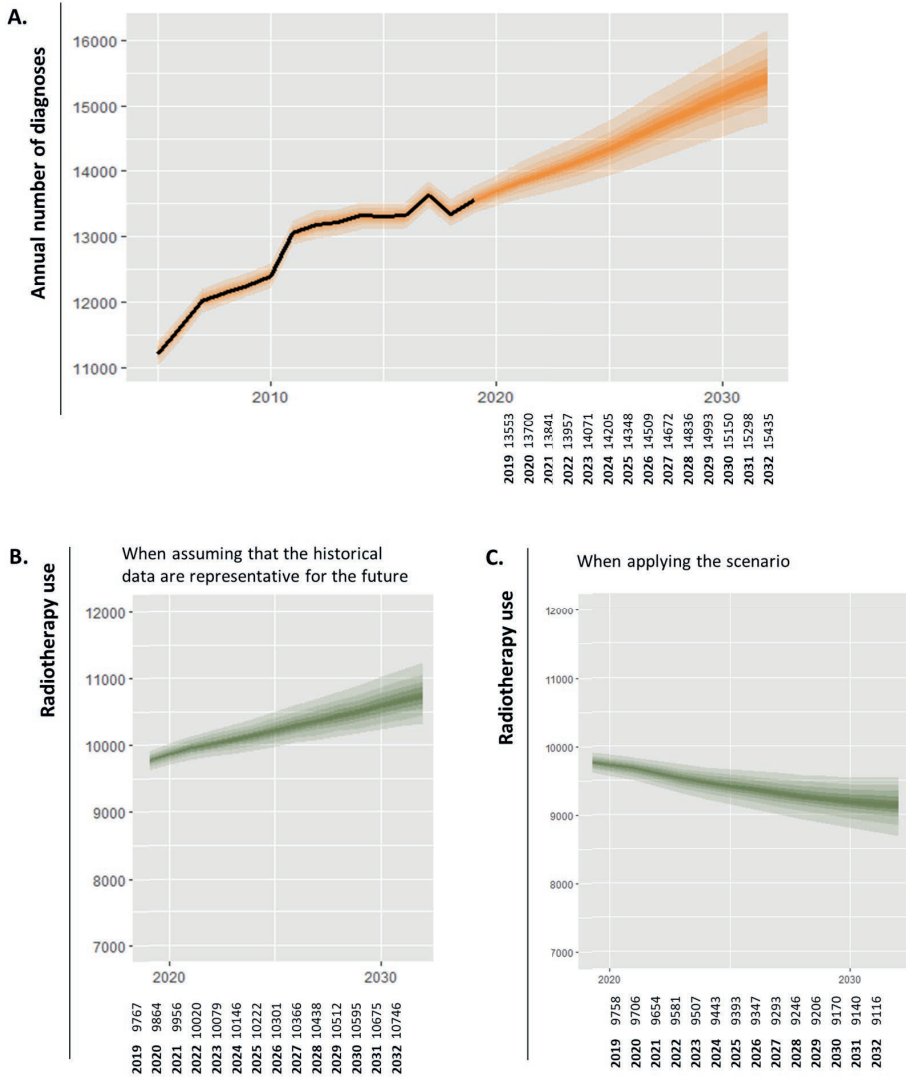**Invasive breast cancer (non-metastatic)**

Figure 11. [A] Forecasted annual number of diagnoses of invasive breast cancer – being the first tumor in the breast, [B] predicted annual number of irradiated patients in future years – assuming the retrospective data being representative, and [C] predicted annual number of irradiated patients in future years in the scenario of continued treatment de-escalation

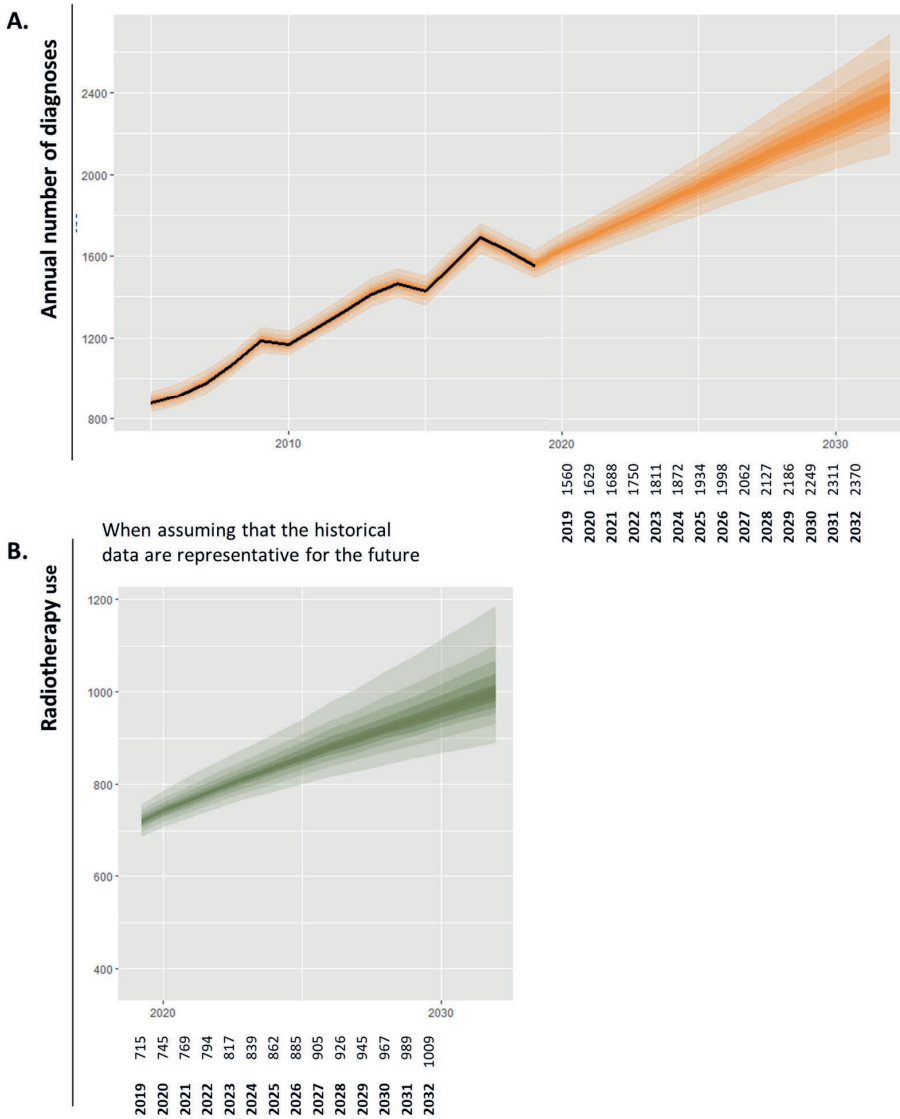**Invasive breast cancer (non-metastatic, not being the first tumor in the breast)**

Figure 12. [A] Forecasted annual number of diagnoses of invasive breast cancer – not being the first tumor in the breast, and [B] predicted annual number of irradiated patients in future years – assuming the retrospective data being representative

Figure 13. [A] Forecasted annual number of localized low-risk prostate cancer diagnoses, [B] predicted annual number of patients receiving EBRT in future years – assuming the retrospective data being representative, [C] predicted annual number of patients receiving brachytherapy in future years – assuming the retrospective data being representative, [D] predicted annual number of patients receiving EBRT in future years in the scenario of (continued) decreasing brachytherapy use and increasing active surveillance, and [E] predicted annual number of patients receiving brachytherapy in future years in the scenario of (continued) decreasing brachytherapy use and increasing active surveillance

Localized intermediate-risk prostate cancer
As classified in the EAU classification for prognostic risk groups and including cT2c tumors with only low- or intermediate-risk features

Figure 14. [A] Forecasted annual number of localized intermediate-risk prostate cancer diagnoses, [B] predicted annual number of patients receiving EBRT in future years – assuming the retrospective data being representative, [C] predicted annual number of patients receiving brachytherapy in future years – assuming the retrospective data being representative, [D] predicted annual number of patients receiving EBRT in future years in the scenario of (continued) decreasing brachytherapy use and decreasing use of prostatectomy, and [E] predicted annual number of patients receiving brachytherapy in future years in the scenario of (continued) decreasing brachytherapy use and decreasing use of prostatectomy
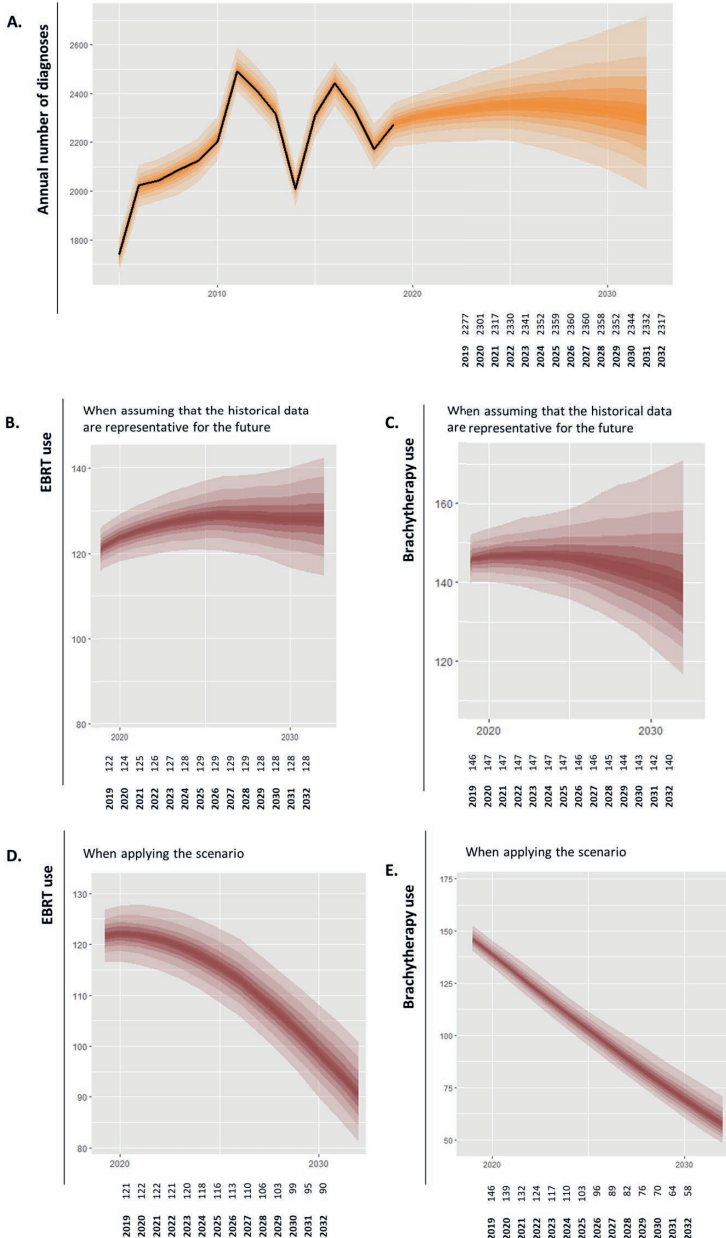
Figure 15. [A] Forecasted annual number of localized high-risk prostate cancer diagnoses, [B] predicted annual number of patients receiving EBRT in future years – assuming the retrospective data being representative, [C] predicted annual number of patients receiving brachytherapy in future years – assuming the retrospective data being representative, [D] predicted annual number of patients receiving EBRT in future years in the scenario of (continued) decreasing brachytherapy use, [E] predicted annual number of patients receiving brachytherapy in future years in the scenario of (continued) decreasing brachytherapy use
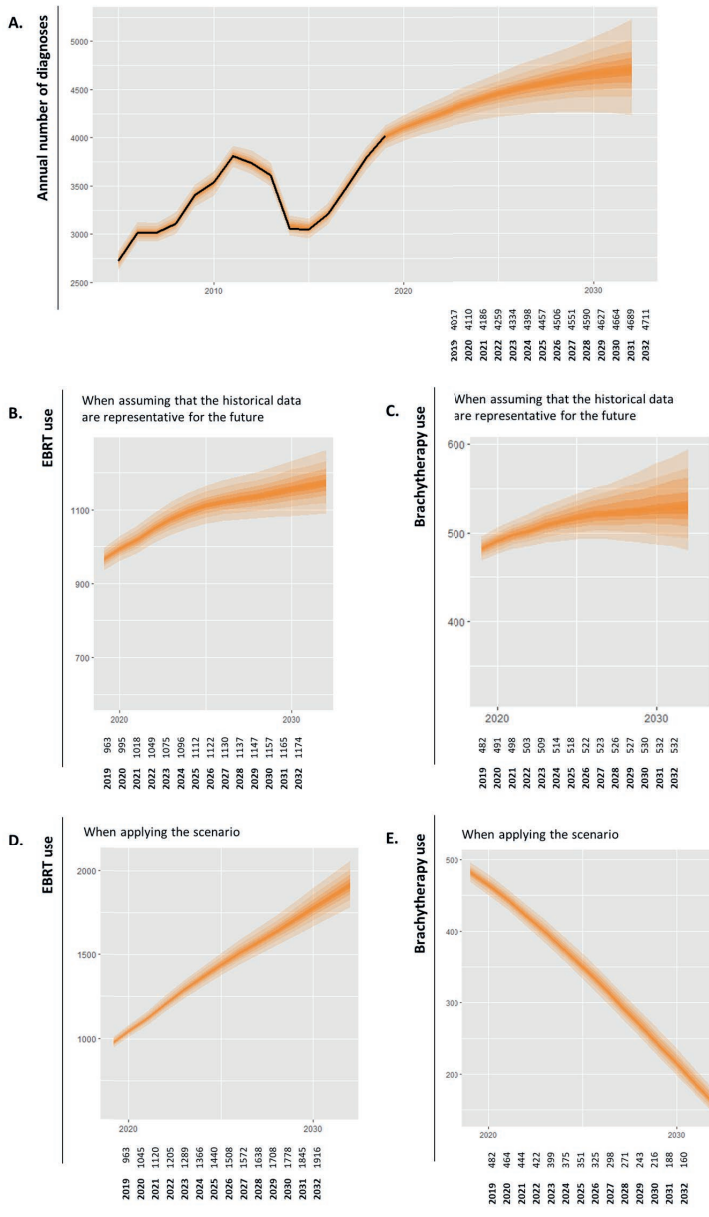
Figure 16. [A] Forecasted annual number of locally advanced prostate cancer diagnoses, [B] predicted annual number of patients receiving EBRT in future years – assuming the retrospective data being representative, [C] predicted annual number of patients receiving brachytherapy in future years – assuming the retrospective data being representative, [D] predicted annual number of patients receiving EBRT in future years in the scenario of (continued) decreasing brachytherapy use, [E] predicted annual number of patients receiving brachytherapy in future years in the scenario of (continued) decreasing brachytherapy use

Rectal cancer

For rectal cancer, the prediction of future radiotherapy use was not stratified for
tumor-specific risk groups, considering the challenges in correctly classifying
the relevant groups (early/intermediate/locally advanced rectal cancer) in the
retrospective data (chapter 7). Hence, the overall future number of all patients
with non-metastatic rectal cancer was predicted. An increase in incidence was
predicted up to 3,438 diagnoses in 2032 (Figure 17A). Of these patients, 1,777 are
predicted to receive radiotherapy in 2032 (Figure 17B). However, the incidence
of rectal cancer has significantly dropped by the introduction of the colorectal
screening program in the Netherlands in 2014. Shortly after introduction, the
incidence increased as a result of diagnosing prevalent cases (which otherwise
would have been diagnosed at a later point in time). Thereafter and up to the
most recent year in our retrospective input data, the incidence decreased as
a result of finding and removing pre-malignant disease stages. The predicted
increase is therefore highly unlikely and illustrates well a limitation of our
framework: the inability of predicting the future in case the retrospective data
are not representative for the future. To provide a more valid number of patients
with non-metastatic rectal cancer receiving radiotherapy, a scenario with a
wide range of possible future incidence numbers for rectal cancer was applied
(Figure 17C). The then estimated number of patients receiving radiotherapy in
2032 is 1,505 and the belonging confidence interval is wide (Figure 17D).

Rectal cancer (non-metastatic)
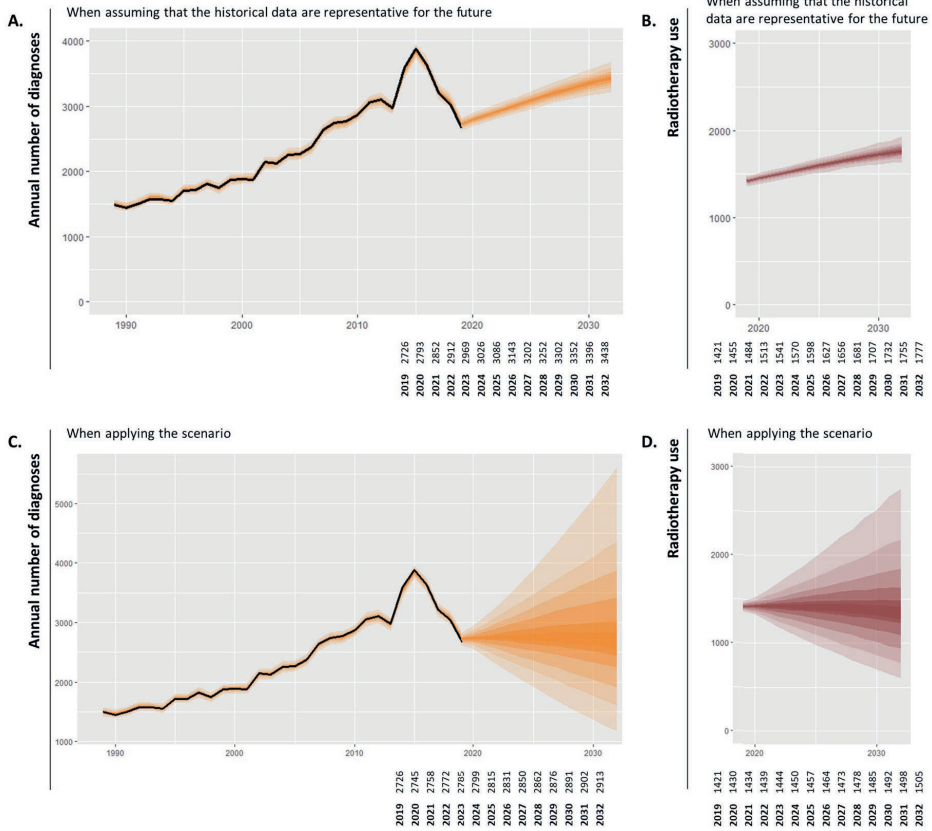
Figure 17. [A] Forecasted annual number of non-metastatic rectal cancer diagnoses, [B] predicted annual number of irradiated patients in future years – assuming the retrospective data being representative, [C] annual number of non-metastatic rectal cancer diagnoses in the scenario of a wide range of possible future incidence numbers, and [D] annual number of irradiated patients in future years in this scenario

Future use of the framework

We have demonstrated the framework by predicting the primary radiotherapy use up to 2032 for all types of non-metastatic cancer, and specifically for non-metastatic stages of NSCLC, DCIS, invasive breast cancer, prostate cancer, and rectal cancer. These predictions based on input data until 2019 should be updated regularly, as new developments continuously change cancer incidence and treatment patterns. Updated data reflecting these developments, may result in changed predictions. In addition to these updates, the methodological framework may in the future be used for predicting radiotherapy use in other types of tumors, or in the same types of tumors while applying other scenarios.

Furthermore, the framework may be applied in predicting future use of other treatment modalities. In all future use of the framework, it is imperative to 1) take into account the number of patients, as a low number would result in highly uncertain predictions, and 2) consider the representativeness to the future of the retrospective data, to prevent false forecasts.

General limitations

In the studies in this thesis and the prediction of future radiotherapy use, data from the population-based Netherlands Cancer Registry were used. These data enabled us to provide nationwide insights in clinical daily practice of radiotherapy use. However, information on palliative treatment in metastatic disease and treatment in recurrent disease, as well as information on dosage and fractionation scheme, are only limited available in the Netherlands Cancer Registry. Hence, our studies were limited to primary treatment in non-metastatic disease. Besides, we could only predict the future number of patients receiving primary radiotherapy. To properly estimate the required future capacity of radiotherapy, insights in fractionation, dosage, and not-primary radiotherapy use is essential. For example, in recent years there has been a strong trend towards hypofractionation with a significantly lower number of fractions per treatment. Detailed insights in fraction schemes, estimates on the proportion of all radiotherapy treatments being primary radiotherapy, together with the predicted number of patients receiving primary radiotherapy, may be useful when ultimately estimating the required future capacity.

The Netherlands Cancer Registry, furthermore, lacks information on preferences regarding treatment. Both preferences of patients and physicians may add to the explanation of the observed treatment variation. In addition, various developments occurred simultaneously. This challenged explaining an observed treatment trend by a certain development, and – the other way around – to assess the effect of a sole development on treatment patterns. These are limitations in the studies in this thesis, which challenged the understanding of the results. Nevertheless, the radiation oncologists and other medical specialists who co-authored the studies helped to get deep understanding of the developments reflected by the observed trends and variations.

In the studies in this thesis, we did not evaluate the use of proton beam radiotherapy, which may be perceived as limitation. Also, future proton beam

radiotherapy use was not predicted using our methodological framework. In the Netherlands, proton beam radiotherapy has recently been introduced and is still in an implementation phase. This challenges a solid interpretation of its effects on radiotherapy treatment patterns, and hampers predicting future proton beam radiotherapy use using the methodological framework. Hence, we chose not to evaluate the use of proton beam radiotherapy in this thesis.

Concluding remarks

The studies in this thesis provide nationwide insights in treatment patterns – with a focus on radiotherapy, which were commissioned by the Dutch Association of Radiotherapy and Oncology. We described changing treatment over time, by *technical developments*, *novel insights in optimal treatment,* and *organizational developments*. Also, (radiotherapy) treatment variation was found between patients, geographical regions, and between different types of hospitals. We aimed to find and explain these trends and variations in the actual treatment patterns, in order to make clinicians and policy makers aware. They can use these insights for evaluating the implementation of technical advancements and new treatment approaches, and when assessing the consequences of organizational changes. In case the insights do not reflect desired trends and variations, clinicians may adjust treatment decision. Potential opportunities for adjusting treatment decision have been illustrated in this general discussion under the title 'What can we learn from treatment patterns?'. We have not assessed the effects of the observed treatment trends and variation on treatment outcomes. This may be interesting to investigate in future studies, which may potentially indicate further possibilities to improve or adjust treatment patterns. Also, we set up a methodological framework to predict the future number of patients receiving primary radiotherapy in non-metastatic stages of cancer. The framework was demonstrated by predicting radiotherapy use in 2032 in various types of tumors. These predictions – together with additional information on radiotherapy in non-metastatic disease, non-primary radiotherapy, and fractionation schemes – may be helpful when estimating the required future capacity of radiotherapy in the Netherlands.

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APPENDICES

A

ENGLISH SUMMARY

NEDERLANDSE SAMENVATTING

DANKWOORD

ABOUT THE AUTHOR

LIST OF PUBLICATIONS

ENGLISH SUMMARY

Radiotherapy is (part of) an eligible curative-intent treatment strategy in various types of non-metastatic cancer, either as single therapy or combined with other treatment modalities like surgery or systemic therapy. However, the eligibility of radiotherapy is continuously changing and therefore the utilization rate of radiotherapy. This thesis provides an overview and tries to explain the nationwide trends and variations of primary radiotherapy use in non-metastatic stages of cancer types often seen at radiotherapeutic facilities: lung cancer – both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), breast cancer – both ductal carcinoma in-situ (DCIS) and invasive breast cancer, prostate cancer, and rectal cancer. The radiotherapy utilization rates were investigated in the broader context of multidisciplinary treatment of these tumor types. Data from the Netherlands Cancer Registry were used to provide these insights. The Netherlands Cancer Registry is a nationwide population-based registry containing information on patient, disease and treatment of all who have been diagnosed with cancer in the Netherlands since 1989.

In **chapter 2**, treatment patterns in patients diagnosed with non-metastatic NSCLC in the period 2008-2018 (N=61,582) were investigated stratified for clinical stage. Surgery has been the traditional preferred treatment strategy in stage I and II NSCLC. However, stereotactic body radiotherapy – delivering high dosage radiation very precisely and therefore being able to destroy small tumors – became increasingly available and was implemented in treatment guidelines as an alternative curative-intent treatment strategy for inoperable patients with stage I disease. In our study period, we observed increased use of radiotherapy, often stereotactic body radiotherapy, in stage I disease: 31% of the patients diagnosed in 2008 was irradiated versus 52% of those diagnosed in 2018. A decreasing number of patients with stage I NSCLC were operated on: 58% in 2008 versus 40% in 2018. This shift in treatment, resulting in radiotherapy being the predominant treatment strategy applied in stage I NSCLC from 2015 on, suggests that (stereotactic body) radiotherapy was also increasingly applied in patients who were not deemed inoperable. In stage II NSCLC, surgery remained the treatment strategy most frequently applied (54%). We found variation in use of radiotherapy versus surgery in stage I-II disease by, among others, age and WHO performance status, which suggest that older and less fit patients were more likely to be irradiated instead of

operated on. In stage III NSCLC, concurrent chemoradiation is the preferred treatment strategy, with sequential chemoradiation as alternative for the more frail patients. Nevertheless, we showed that only 35% of the patients diagnosed with stage III NSCLC in 2008 and 39% of those diagnosed in 2018 received both chemotherapy and radiotherapy – most often concurrently (72%). Variation in the chemoradiation scheme was observed for age and performance status – suggesting less intensive treatment for older and less fit patients, as well as for regions in the Netherlands – which may reflect unwarranted variation between clinical practices across the country.

SCLC accounts for approximately 12% of all lung cancer diagnoses globally, often presenting with metastasis (stage IV) or at locally advanced stage (stage III) at the time of diagnosis. Treatment patterns in patients diagnosed with non-metastatic SCLC in the period 2008-2019 (N=6,578) were investigated in **chapter 3**. While chemoradiation is the cornerstone of curative-intent treatment in non-metastatic SCLC, surgery and stereotactic body radiotherapy – both followed by chemotherapy – are nowadays also considered as curative-intent treatment strategy in very early stages (T1-2N0 tumors). In clinical stage I SCLC, we observed decreasing combined use of chemotherapy and radiotherapy: administered to 47% of patients diagnosed in 2008-2009 versus 15% of those diagnosed in 2018-2019. Meanwhile, use of surgery increased from 29% to 44%, as did use of (stereotactic body) radiotherapy from 8% to 22%. The percentage of patients receiving both chemotherapy and radiotherapy remained stable in stage II (64%) and increased in stage III – from 57% of patients diagnosed in 2008 to 70% of those diagnosed in 2019. Most stage II-III patients received concurrent chemoradiation, since 2012 mainly with hyperfractionated accelerated radiotherapy. The strongest associated with concurrent versus sequential chemoradiation in stage II-III SCLC were period of diagnosis – reflecting increased use of the concurrent scheme, and age and performance status – reflecting treatment decision based on patient frailty. Furthermore, patients with worse performance status were less likely to receive accelerated radiotherapy in context of concurrent chemoradiation. The use of accelerated versus conventionally fractionated radiotherapy in concurrent chemoradiation was also associated with region, radiotherapy facility volume and availability of a radiotherapy department in the hospital of diagnosis – all reflecting a lack of uniform treatment decision across the Dutch hospitals regarding radiotherapy fractionation schemes in SCLC.

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The evolving treatment patterns for women diagnosed with DCIS in 2008-2022 (N=30,187), particularly the de-intensification efforts, were investigated in **chapter 4**. DCIS is traditionally treated with breast-conserving surgery followed by radiotherapy, or mastectomy. However, a significant portion of DCIS may not progress to invasive cancer. Hence, ongoing efforts aim to shift treatment towards personalized and less invasive approaches to manage DCIS. In line with these efforts, we observed decreased mastectomy rates in DCIS and increased omission of radiotherapy following breast-conserving surgery in DCIS grade I-II – from ~11% in those diagnosed until 2013 to ~26% since 2017. Thereafter, omission of surgery rose from 8% in 2017 to 30% in 2022 in grade I-II. In grade III, omission of surgery was limited and use of breast-conserving surgery without radiotherapy only slightly increased from ~3% until 2015 to 7% in 2022. Age, lesion size, and resection margin status were significantly associated with use of radiotherapy following breast-conserving surgery, indicating tailoring of treatment towards patients' risk of (invasive) recurrence. In women who did receive radiotherapy following breast-conserving surgery, use of boost irradiation decreased. We found risk-increasing factors as young age, a larger lesion, and an irradical resection to be associated with boost-use. In addition to factors related to risk of recurrence, we found hospital-characteristics to be associated with post-breast-conserving surgery (boost) radiotherapy, which may reflect (implementation differences in) shared-decision making. In DCIS grade I-II, radiotherapy de-intensification was furthermore seen by a shift from whole breast irradiation to partial breast irradiation.

In **chapter 5**, trends and variations in radiotherapy use as part of multimodal treatment for invasive non-metastatic breast cancer were investigated in women diagnosed in 2008-2019 (N=176,292). Like in DCIS, we observed treatment de-intensification by decreased use of mastectomy, which coincided with increased use of breast-conserving surgery with radiotherapy – administered to 48% in those diagnosed in 2008 versus 56% since 2016. After 2016, radiotherapy was increasingly omitted in older patients who underwent breast-conserving surgery; the overall use of breast-conserving surgery without radiotherapy increased from 4% in 2016 to 9% in 2019. Further treatment de-intensification was noted by decreasing use of boost irradiation and increasing use of partial breast irradiation. Boost irradiation in breast-conserving therapy was associated with high-risk features as younger age, higher grade, residual disease, lymph node metastases, or higher T-stage. In

patients with nodal involvement, traditional axillary lymph node dissection was decreasingly applied (76% in 2011, 24% in 2019) and replaced by regional radiotherapy (32% in 2011, 61% in 2019). Women with more advanced disease (lymph node macrometastatic versus micrometastatic disease, higher T-stage, higher grade) were less likely to be treated with regional radiotherapy instead of axillary lymph node dissection. The observed trends and variations reflect evolving treatment guidelines, with an increased focus on personalized and less intensive approaches to radiotherapy in specific patient groups. Also variations in boost irradiation and regional treatment were observed between regions in the country, which possibly reflect differences in local treatment protocols.

In non-metastatic prostate cancer various treatment strategies can be considered, depending on the risk group. In **chapter 6**, treatment patterns were investigated in men diagnosed in 2008-2019 with localized low-, intermediate- or high-risk disease, or locally advanced disease (N=103,059). In low-risk prostate cancer, treatment guidelines prescribe active surveillance instead of direct treatment since 2009/2010. In line with this policy, we observed an increasing number of patients receiving no active treatment – 55% of those diagnosed with low-risk disease in 2008 compared to 73% in 2019. Coincidingly, brachy-monotherapy and radical prostatectomy were decreasingly applied, while use of external beam radiotherapy remained stable over time. We found higher T-stage to be associated with use of radiotherapy instead of no active treatment. Also, variation across the country and associations with age were found: younger compared to older men more likely received brachy-monotherapy instead of no active treatment, while older compared to younger men more likely received external beam radiotherapy instead of no active treatment. In intermediate- and high-risk prostate cancer, including locally advanced disease, patients' preferences and tumor characteristics should determine treatment decision between external beam radiotherapy, radical prostatectomy, and brachy-monotherapy (the latter only in intermediate-risk disease), as high-quality evidence on superiority of one of the treatment strategies is lacking. In intermediate-risk disease, brachy-monotherapy use decreased, which coincided with increased radical prostatectomy use in 2008-2011, which thereafter decreased, and increased use of external beam radiotherapy since 2014. These trends coincided with the introduction of a volume norm for prostatectomies, decreased availability of facilities offering brachytherapy and increased availability of facilities offering

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external beam radiotherapy. In high-risk disease, external beam radiotherapy and radical prostatectomy were increasingly applied, while non-curative hormonal-monotherapy use decreased. Higher age, more comorbidities and less travel time for radiotherapy were positively associated with external beam radiotherapy versus radical prostatectomy in intermediate and high-risk prostate cancer – indicating treatment decision tailored to the patients' frailty and probably preferences. Furthermore, treatment modalities available at the diagnostic hospital appeared to be associated with treatment decision. The observed trends suggest evolving practices, influenced by changes in treatment guidelines, and the availability of radiotherapy and hospitals performing prostatectomies.

In **chapter 7**, trends and variations in radiotherapy use as part of multimodal treatment for early, intermediate, and locally advanced rectal cancer were investigated in patients diagnosed in 2008-2021 (N=37,510). Surgery has been the standard treatment for non-metastatic rectal cancer, with neoadjuvant (chemo)radiotherapy for downstaging and reducing locoregional recurrence risk. However, interest in organ-sparing treatment increased – mainly in locally advanced disease, as well as interest in tailoring neoadjuvant treatment to the risk of poor prognosis. In line with these developments, use of neoadjuvant chemoradiation or radiotherapy in early rectal cancer decreased – the latter from 61% in those diagnosed in 2008 to 7% in 2021, while use of surgery without neoadjuvant treatment increased. Due to the colorectal cancer screening program implementation, the number of early cases treated with endoscopic resection also increased. In intermediate rectal cancer, neoadjuvant treatment shifted from chemoradiation to radiotherapy, with older patients, those with more comorbidities, and a poorer performance status being more likely to receive the less intensive neoadjuvant radiotherapy. In locally advanced disease, surgery was increasingly omitted following chemoradiation – pointing out the ongoing paradigm shift. This organ-preserving strategy was received by 2-4% of patients diagnosed until 2013 versus 17% in 2019-2021. Use of treatment strategies for improving chance of a complete remission by chemoradiation also increased. Regional variation was found both in neoadjuvant treatment in intermediate disease as well as in use of surgery following chemoradiation in locally advanced disease, indicating regional differences in uptake of new treatment strategies.

NEDERLANDSE SAMENVATTING

Radiotherapie is (onderdeel van) een geschikte curatieve behandelingsoptie bij verschillende soorten niet-gemetastaseerde kanker, zowel als monotherapie of gecombineerd met andere behandelingen zoals chirurgie of systemische therapie. De geschiktheid van radiotherapie verandert echter voortdurend en daarmee ook het gebruik van radiotherapie. Dit proefschrift geeft een overzicht en probeert verklaringen te geven voor de landelijke trends en variaties in het gebruik van primaire radiotherapie bij niet-gemetastaseerde stadia van kankersoorten die vaak gezien worden bij radiotherapiefaciliteiten: longkanker – zowel niet-kleincellige longkanker (NSCLC) als kleincellige longkanker (SCLC), borstkanker – zowel ductaal carcinoom in situ (DCIS) als invasieve borstkanker, prostaatkanker en rectumkanker. Het gebruik van radiotherapie werd onderzocht in de bredere context van multidisciplinaire behandeling van deze tumortypes. Gegevens uit de Nederlandse Kankerregistratie werden gebruikt om deze inzichten te verschaffen. De Nederlandse Kankerregistratie is een landelijke registratie met informatie over patiënten, ziekte en behandeling van iedereen die sinds 1989 in Nederland is gediagnosticeerd met kanker.

In **hoofdstuk 2** werden behandeltrends bij patiënten gediagnosticeerd met niet-gemetastaseerde NSCLC in de periode 2008-2018 (N=61.582) onderzocht, gestratificeerd naar klinisch stadium. Chirurgie is traditioneel de voorkeursbehandelingsstrategie bij stadium I en II NSCLC. Stereotactische radiotherapie – waarbij een hoge stralingsdosis zeer nauwkeurig wordt afgegeven, wat in staat stelt kleine tumoren te vernietigen – is echter steeds meer beschikbaar gekomen en geïmplementeerd in behandelrichtlijnen als alternatieve curatieve behandelingsstrategie voor niet-operabele patiënten met stadium I-ziekte. In onze onderzoeksperiode zagen we bij stadium I-ziekte een toename in het gebruik van radiotherapie, vaak stereotactische radiotherapie: 31% van de patiënten gediagnosticeerd in 2008 werd bestraald t.o.v. 52% in 2018. Een afnemend aantal patiënten met stadium I NSCLC ondergingen een operatie: 58% in 2008 t.o.v. 40% in 2018. Deze verschuiving in behandeling, resulterend in radiotherapie als de meest toegepaste behandeling bij stadium I NSCLC vanaf 2015, suggereert dat (stereotactische) radiotherapie ook steeds vaker werd toegepast bij patiënten die niet als niet-operabel werden beschouwd. In stadium II NSCLC bleef chirurgie de meest toegepaste behandelstrategie (54%). We vonden variatie in het gebruik van radiotherapie t.o.v. chirurgie bij

stadium I-II-ziekte voor onder andere leeftijd en WHO-performancestatus, wat suggereert dat oudere en minder fitte patiënten eerder werden bestraald dan geopereerd. In stadium III NSCLC is gelijktijdige ("concurrent") chemoradiatie de behandelstrategie van voorkeur, met sequentiële chemoradiatie als alternatief voor de meer kwetsbare patiënten. Desondanks toonden we aan dat slechts 35% van de patiënten gediagnosticeerd met stadium III NSCLC in 2008 en 39% van degenen gediagnosticeerd in 2018 zowel chemotherapie als radiotherapie kreeg – meestal gelijktijdig (72%). Variatie in het chemoradiatieschema werd gevonden voor leeftijd en performancestatus – wat wijst op minder intensieve behandeling voor oudere en minder fitte patiënten, evenals voor regio's in Nederland – wat mogelijk ongerechtvaardigde praktijkvariatie in het hele land weerspiegelt.

SCLC vertegenwoordigt ongeveer 12% van alle longkankerdiagnoses wereldwijd en presenteert zich vaak met metastase (stadium IV) of in lokaal gevorderd stadium (stadium III). Behandelpatronen bij patiënten gediagnosticeerd met niet-gemetastaseerde SCLC in de periode 2008-2019 (N=6.578) werden onderzocht in **hoofdstuk 3**. Hoewel chemoradiatie de hoeksteen is van curatieve behandeling bij niet-gemetastaseerde SCLC, worden chirurgie en stereotactische radiotherapie – beide gevolgd door chemotherapie – tegenwoordig ook beschouwd als curatieve behandelingsstrategieën bij zeer vroege stadia (T1-2N0-tumoren). In klinisch stadium I SCLC zagen we een afname in het gecombineerde gebruik van chemotherapie en radiotherapie: toegediend aan 47% van de patiënten gediagnosticeerd in 2008-2009 t.o.v. 15% in 2018-2019. Ondertussen nam het gebruik van chirurgie toe van 29% tot 44%, evenals het gebruik van (stereotactische) radiotherapie van 8% tot 22%. Het percentage patiënten dat zowel chemotherapie als radiotherapie kreeg bleef stabiel in stadium II (64%) en nam toe in stadium III – van 57% van de patiënten gediagnosticeerd in 2008 tot 70% in 2019. De meeste patiënten met stadium II-III kregen gelijktijdige ("concurrent") chemoradiatie, sinds 2012 voornamelijk met hypergefractioneerde geaccelereerde radiotherapie. De sterkste associatie met gelijktijdige t.o.v. sequentiële chemoradiatie bij stadium II-III SCLC werd gevonden voor periode van diagnose – wat wijst op toegenomen gebruik van het gelijktijdige schema, en voor leeftijd en performancestatus – wat wijst op een behandelkeuze op basis van de kwetsbaarheid van de patiënt. Bovendien kregen patiënten met een slechtere performancestatus minder vaak geaccelereerde radiotherapie in de context van gelijktijdige chemoradiatie. Het

gebruik van geaccelereerde t.o.v. conventioneel gefractioneerde radiotherapie bij gelijktijdige chemoradiatie was ook geassocieerd met regio, het volume van de radiotherapiefaciliteit en beschikbaarheid van een radiotherapieafdeling in het ziekenhuis van diagnose. Deze zaken wijzen op een gebrek aan uniforme behandelbeslissing t.a.v. radiotherapie-fractioneringsschema's in de behandeling van SCLC.

De behandelpatronen voor vrouwen gediagnosticeerd met DCIS in 2008-2022 (N=30.187), met name de inspanningen voor de-intensificatie van behandeling, werden onderzocht in **hoofdstuk 4**. DCIS wordt traditioneel behandeld met borstsparende chirurgie gevolgd door radiotherapie, of mastectomie. Een aanzienlijk deel van DCIS zal zich echter niet ontwikkelen tot invasieve kanker. Daarom zijn er voortdurende inspanningen om DCIS op een meer gepersonaliseerde en minder invasieve manier te behandelen. In lijn met deze inspanningen zagen we een afname in het gebruik van mastectomie bij DCIS en het toenemend achterwege laten van radiotherapie na borstsparende chirurgie bij DCIS graad I-II – van ~11% bij degenen gediagnosticeerd tot 2013 tot ~26% sinds 2017. Daarna werd chirurgie bij een toenemend deel van de patiënten met DCIS graad I-II achterwege gelaten – bij 8% in 2017 tot 30% in 2022. Bij graad III was het weglaten van chirurgie beperkt en het gebruik van borstsparende chirurgie zonder radiotherapie steeg slechts licht van ~3% tot 2015 tot 7% in 2022. Leeftijd, laesiegrootte en resectiemarges waren geassocieerd met het gebruik van radiotherapie na borstsparende chirurgie, wat wijst op het afstemmen van de behandeling op het risico op (invasieve) terugkeer. Bij vrouwen die wel radiotherapie ontvingen na borstsparende chirurgie, nam het gebruik van boost-bestraling af. Risico verhogende factoren zoals jongere leeftijd, een grotere laesie en een niet-radicale resectie bleken geassocieerd met het gebruik van boost-bestraling. Naast factoren gerelateerd aan het risico op terugkeer, bleken ziekenhuiskenmerken geassocieerd te zijn met (boost-)bestraling na borstsparende chirurgie, wat mogelijk (implementatieverschillen in) shared decision making weerspiegelt. Bij DCIS graad I-II werd ook de-intensificatie van radiotherapeutische behandeling gezien door een verschuiving van gehele borstbestraling naar gedeeltelijke borstbestraling.

In **hoofdstuk 5** werden trends en variaties in het gebruik van radiotherapie als onderdeel van multimodale behandeling voor invasieve niet-gemetastaseerde borstkanker onderzocht bij vrouwen gediagnosticeerd

in 2008-2019 (N=176.292). Zoals bij DCIS zagen we de-intensificatie van behandeling door afgenomen gebruik van mastectomie, wat samenviel met een toename in het gebruik van borstsparende chirurgie met radiotherapie – toegediend aan 48% bij degenen gediagnosticeerd in 2008 t.o.v. 56% sinds 2016. Na 2016 werd radiotherapie steeds vaker achterwege gelaten bij oudere patiënten die borstsparende chirurgie ondergingen; het totale gebruik van borstsparende chirurgie zonder radiotherapie nam toe van 4% in 2016 tot 9% in 2019. Verdere de-intensificatie van behandeling bleek uit het afgenomen gebruik van boost-bestraling en toegenomen gebruik van gedeeltelijke borstbestraling. Boost-bestraling bij borstsparende therapie was geassocieerd met hoog risico-factoren zoals jonge leeftijd, hogere graad, resterende ziekte, lymfekliermetastasen of hoger T-stadium. Bij patiënten met - lymfekliermetastasen werd traditionele axillaire lymfeklierdissectie steeds minder toegepast (76% in 2011, 24% in 2019) en vervangen door regionale radiotherapie (32% in 2011, 61% in 2019). Vrouwen met gevorderdere ziekte (lymfeklier-macro-metastatische versus micro-metastatische ziekte, hoger T-stadium, hogere graad) kregen minder vaak regionale radiotherapie in plaats van axillaire lymfeklierdissectie. De geobserveerde trends en variaties weerspiegelen veranderende behandelrichtlijnen, met toenemende focus op gepersonaliseerde en minder intensieve benaderingen van radiotherapie bij specifieke patiëntengroepen. Ook werden variaties in boost-bestraling en regionale behandeling waargenomen tussen regio's in het land, wat mogelijk verschillen in lokale behandelprotocollen weerspiegelt.

Bij niet-gemetastaseerde prostaatkanker kunnen verschillende behandelstrategieën worden overwogen, afhankelijk van de risicogroep. In **hoofdstuk 6** werden behandeltrends onderzocht bij mannen gediagnosticeerd in 2008-2019 met gelokaliseerde laag-, intermediair- of hoog-risico ziekte, of lokaal gevorderde ziekte (N=103.059). Bij laag-risico prostaatkanker schrijven behandelrichtlijnen sinds 2009/2010 een actief volgen-beleid voor in plaats van directe behandeling. In lijn met dit beleid zagen we een toenemend aantal patiënten dat geen actieve behandeling kreeg – 55% van degenen gediagnosticeerd met laag-risico ziekte in 2008 vergeleken met 73% in 2019. Tegelijkertijd werden brachy-monotherapie en radicale prostatectomie minder toegepast, terwijl het gebruik van uitwendige radiotherapie stabiel bleef. Een hoger T-stadium bleek geassocieerd met het gebruik van radiotherapie in plaats van geen actieve behandeling. Ook werden variaties door het hele

land en associaties met leeftijd gevonden: jongere mannen kregen eerder brachy-monotherapie in plaats van geen actieve behandeling dan oudere mannen, terwijl oudere mannen eerder uitwendige radiotherapie kregen in plaats van geen actieve behandeling dan jongere mannen. Bij intermediair- en hoog-risico prostaatkanker, inclusief lokaal gevorderde ziekte, zou de behandelkeuze tussen uitwendige radiotherapie, radicale prostatectomie en brachy-monotherapie (de laatste alleen bij intermediaire risicoziekte) moeten afhangen van de voorkeuren van patiënten en tumorkenmerken, aangezien hoogwaardig bewijs over de superioriteit van één van de behandelstrategieën ontbreekt. Bij intermediair-risico ziekte nam het gebruik van brachy-monotherapie af, wat samenviel met een toename in het gebruik van radicale prostatectomie in 2008-2011, wat daarna afnam, en een toename in het gebruik van uitwendige radiotherapie sinds 2014. Deze trends vielen samen met de introductie van een volumenorm voor prostatectomie, een afname in de beschikbaarheid van faciliteiten die brachytherapie aanbieden en een toename in de beschikbaarheid van faciliteiten die uitwendige radiotherapie aanbieden. Bij hoog-risico ziekte werden uitwendige radiotherapie en radicale prostatectomie steeds vaker toegepast, terwijl het gebruik van niet-curatieve hormonale monotherapie afnam. Hogere leeftijd, meer comorbiditeiten en minder reistijd voor radiotherapie waren geassocieerd met uitwendige radiotherapie in plaats van radicale prostatectomie bij intermediair- en hoog-risico prostaatkanker – wat erop wijst dat bij de behandelkeuze rekening wordt gehouden met de kwetsbaarheid en waarschijnlijk voorkeuren van de patiënt. Bovendien bleek de beschikbaarheid van behandelmodaliteiten in het ziekenhuis van diagnose geassocieerd met behandelkeuze. De geobserveerde trends suggereren veranderende behandeling van prostaatkanker, beïnvloed door veranderingen in behandelrichtlijnen, en de beschikbaarheid van radiotherapie en ziekenhuizen die prostatectomieën uitvoeren.

In **hoofdstuk 7** werden trends en variaties in het gebruik van radiotherapie als onderdeel van multimodale behandeling voor vroege, intermediaire en lokaal gevorderde rectumkanker onderzocht bij patiënten gediagnosticeerd in 2008-2021 (N=37.510). Chirurgie is de standaardbehandeling voor niet-gemetastaseerde rectumkanker, met neoadjuvante (chemo)radiotherapie voor *downstaging* en het verminderen van het risico op locoregionaal recidief. Er is echter toenemende interesse in orgaansparende behandeling – voornamelijk bij lokaal gevorderde ziekte, evenals inspanningen om

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neoadjuvante behandeling af te stemmen op het risico op een slechte prognose. In lijn met deze ontwikkelingen, nam het gebruik van neoadjuvante chemoradiatie of radiotherapie bij vroege rectale kanker af – radiotherapie van 61% bij degenen gediagnosticeerd in 2008 tot 7% in 2021, terwijl het gebruik van chirurgie zonder neoadjuvante behandeling toenam. Als gevolg van de implementatie van de colorectale screening nam ook het aantal vroege stadia diagnosen behandeld met endoscopische resectie toe. Bij intermediair rectumkanker verschoof neoadjuvante behandeling van chemoradiatie naar radiotherapie, waarbij oudere patiënten, patiënten met meer comorbiditeiten en een slechtere performancestatus eerder de minder intensieve neoadjuvante radiotherapie kregen. Bij lokaal gevorderde ziekte werd de chirurgie steeds vaker weggelaten na chemoradiatie – wat wijst op de veranderd behandelparadigma. Deze orgaanbesparende strategie werd toegepast bij 2-4% van de patiënten gediagnosticeerd tot 2013 t.o.v. 17% in 2019-2021. Het gebruik van behandelingen om de kans op een volledige remissie te verbeteren door chemoradiatie nam ook toe. Er werd regionale variatie gevonden in zowel neoadjuvante behandeling bij intermediaire ziekte als in het gebruik van chirurgie na chemoradiatie bij lokaal gevorderde ziekte, wat wijst op regionale verschillen in de acceptatie van nieuwe behandelstrategieën.

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ABOUT THE AUTHOR

Jelle Evers was born on the first of July, 1994 in Lettele, the Netherlands. After graduating from pre-university education at Etty Hillesum Lyceum in Deventer in 2012, he started his Bachelor's degree in Biomedical Sciences at the Radboud University in Nijmegen. He published the results from his research internship on the degree of consensus among healthcare professionals for support of cancer patients' lifestyle management, performed at the Health Evidence department of the Radboudumc, was board member of the students' representation, and graduated in 2015. Jelle continued with his Master's studies Biomedical Sciences at the Radboud University and specialized in Epidemiology (major) and Health Technology Assessment (minor). In his final research internship at the Health Evidence department, he investigated and published on the associations of obesity and Diabetes Mellitus with bladder cancer recurrence and progression. In the final year of his Master's degree he broadened his scope with a consultancy profile and successfully completed his internship at Philips Research in Eindhoven, delivering a well-endorsed advice on scalable health coaching and medical support in Philips' health propositions. Jelle graduated with honors from his Master's studies in 2017. Thereafter he started working as a researcher at the PHARMO Institute in Utrecht, performing (among others) Post-Authorisation Safety Studies (PASS) in close collaboration with pharmaceutical stakeholders.

In 2020, Jelle started his PhD-research at the Netherlands Comprehensive Cancer Organisation (IKNL) in Eindhoven and Utrecht, in collaboration with the University of Twente in Enschede. His PhD-research focused on trends and variations in radiotherapy use in the context of multimodal treatment for various types of tumors, and was performed in close collaboration with the Dutch Association of Radiation Oncology (NVRO). The results of his PhD-research are presented in this thesis. Jelle presented his work at several international and national conferences, supervised students doing research internships, and started a PhD-council at IKNL together with 3 other PhD-candidates. Currently, he is continuing his work at IKNL as a Clinical Data Scientist, with a focus on Public Health & Prevention and international studies using the OMOP-common data model.

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< Total radiotherapy
in stage I NSCLC

Brachymonotherapy in >
low-risk prostate cancer

< Total radiotherapy in
invasive M0 breast cancer

Breast conserving surgery with >
radiotherapy in DCIS grade I-II

< Chemoradiation in locally
advanced rectal cancer

Total radiotherapy >
in stage I SCLC