Variation in the Use of Radiotherapy for Cancer Patients

Population-based Studies in the South of the Netherlands

Variatie in het gebruik van radiotherapie voor kankerpatiënten

Population-based studies in het zuiden van Nederland

Ans Vulto

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Voor mijn vader

Contents

Chapter 1

Introduction

1.1 Background

Since the 1950's and especially since the 70's upon the introduction of megavoltage radiotherapy plays a growing and more important role in the treatment of cancer, especially in breast, rectal, prostate and lung cancer and lymphoma. With curative intention it can be part of the primary treatment, often in combination with surgery and/or chemotherapy or it can be used for treatment of recurrence. In palliation, either as primary treatment or in case of recurrence or metastases, a short course of radiotherapy often relieves pain or other symptoms.[1]

Of all newly diagnosed cancer patients about 50% are generally assumed to receive radiotherapy during the course of their disease.[2, 3] This percentage is only an estimation but is nevertheless often used in the process of decision making to plan the future capacity of radiotherapy equipment and personnel needed. It consists of a mixture of immediate radiotherapy (as part of the primary treatment) and delayed (or secondary) radiotherapy.

In Australia a technique was developed to estimate the ideal proportion of new cases of cancer that should receive radiotherapy at least once during the course of their illness based on the best available evidence, which was 52%.[4]

Population-based studies, however, (which are hardly done in the field of radiotherapy use or outcome) give a real insight in the use of radiotherapy. They are also essential to explore trends in time. And they might be very suitable to extrapolate the consumption of radiotherapy in the future, which will provide a contribution to planning and programming the required capacity of equipment and personnel.[5]

Population-based studies of the use of radiotherapy for different tumour types, preferably by stage and age, can also illustrate necessary as well as arbitrary changes in treatment and provide an impression of adherence to guidelines.

Guidelines

In the Netherlands treatment guidelines have been developed for most tumour types since the 80's; first at institutional and regional, then at national, and nowadays more and more at international level, increasingly evidence-based. At national level guideline development through the Dutch Institute for Healthcare Improvement (CBO) went from consensus and expert-based to evidence-based.[6]

For example, for patients with *breast cancer*, radiotherapy is an indispensable part of breast-conserving treatment.[6] About 75% of all patients with stage I or IIa disease are eligible for breast-conserving treatment, while only half of these patients receive conserving surgery.[7] Postoperative radiotherapy after mastectomy decreases the risk of loco regional recurrence and is associated with improved survival in high-risk breast cancer patients.[8-11]

In patients with stage III or IV *lung cancer* and low performance status, weight loss or locally too advanced disease radiotherapy can accomplish a decline in tumour load which reduces symptoms.[12]

In recent years, for patients with locally advanced (stage III) lung cancer the standard treatment (with curative intent) is a combination of chemotherapy and radiotherapy.[6, 13]

The standard treatment for operable *rectal cancer* stage T3 and/or N1 was postoperative radiotherapy. Since the 1980's the role of preoperative radiotherapy was extensively examined,[14, 15] based on the more thorough total mesorectal excision (TME) without any positive margins, and some departments in the Netherlands started with preoperative radiotherapy in the early/mid 90's.[16, 17] Between 1996 and 2001 many Dutch patients with rectal cancer were treated within the framework of the Dutch TME-trial, in which randomisation occurred between total mesorectal excision with or without RT.[18] Since 2001 the standard treatment for patients with resectable rectal cancer (except for T1 tumours) is a short course of preoperative radiotherapy.[6]

Treatment options for patients with localised *prostate cancer* are, besides watchful waiting, radical prostatectomy, external beam radiotherapy or brachytherapy, often depending on the preference of the urologist.[6, 19] Patients with a locally advanced tumour may be treated with radical prostatectomy or external beam radiotherapy, both with or without hormonal therapy, or hormonal therapy alone.[6, 20]

Postoperative radiotherapy was controversial in patients with *endometrial cancer* stage I[21] (for stage II and III postoperative radiotherapy is standard treatment). From the results of the Portec-Trial, studying the value of radiotherapy for patients with stage I endometrial cancer,[22] guidelines were developed: postoperative radiotherapy is indicated for patients older than 60 years with stage Ia and Ib grade 3 or with stage Ic and for patients younger than 60 years with stage Ic grade 3.[6]

Variations in treatment

Despite guidelines, large variations in the management of patients with cancer were seen in the USA and Europe between regions, hospitals and surgical units.[19, 23-29] These variations can be explained partly by differences in management protocols between treatment units or hospitals, by preferences of specialists (i.e. due to deficient knowledge of or disagreement with guidelines) or by patient characteristics such as age or co-morbid conditions as well as individual preferences of patients. In the Netherlands variations between hospitals in referral for radiotherapy were never studied before.[21]

In elderly patients therapy may be less aggressive.[30, 31] There might be several reasons for older patients why they should not endure radiotherapy, such as the distance to the radiotherapy facility and the long duration of the therapy (often 6-7 weeks for curative therapy), the fear for more severe side effects and the possibility of social disturbances such as disorientation or anxiety. Because elderly patients are often excluded from clinical trials, effects are not always well known, or only in healthy elderly. It is therefore more complex to choose the optimal treatment for elderly patients. Nevertheless, radiotherapy should not be withheld because of chronological age alone.[31-33]

Serious co-morbidity is present in more than 50 percent of patients aged 60 years or older with cancer.[34, 35] For patients with serious co-morbidity, the standard oncological treatment might be altered because of an increased risk of complications or a limited life expectancy for non-oncologic reasons. To study the influence of age and/or co-morbidity on receiving radiotherapy, a population-based setting is very convenient.

Secondary and palliative radiotherapy

Radiotherapy plays an important role in palliation. For example, radiotherapy is the treatment of choice for most patients with spinal cord compression;[36] it should be initiated as soon as possible to optimise the chances for restoration of neurological function. A survey among general practitioners in Canada showed that many physicians were unaware of the effectiveness of radiotherapy in palliative situations like spinal cord compression, haemoptysis, haematuria and brain metastases.[37] Research among Dutch general practitioners seemed to confirm this.[38]

In the literature most population-based studies only describe radiotherapy as part of the primary treatment. The estimated percentages are a combination of radiotherapy as part of the primary treatment and delayed radiotherapy. No reliable impression is given of the cumulative proportion of patients receiving delayed or secondary radiotherapy,[2] although this may contribute substantially to the total radiotherapy consumption. A real insight can be given in primary and secondary radiotherapy for patients in a cohort during the time they are followed and such data become comparable when this cohort is population-based.

1.2 Patients and Methods

Eindhoven Cancer Registry

The Eindhoven Cancer Registry (ECR) was started in 1955 as part of a program for nation-wide cancer registration in the area of South-Eastern North Brabant. Data on all new cancer patients were collected directly from pathology reports and patients' medical records. The registry was started in three hospitals in Eindhoven and gradually expanded into the south-east of North Brabant, the northern part of the province of Dutch Limburg (since 1970) and, following the foundation of the Comprehensive Cancer Centre South (Integraal Kankercentrum Zuid, IKZ), the middle, north eastern and south-western part of North Brabant since 1986 (except the most western part) (figure 1).

In the rest of the Netherlands, other regional registries had discontinued their activities, until a successful nation wide program was re-established since 1984. Since 1989 the whole Dutch population is covered by nine regional cancer registries, which established the Netherlands Cancer Registry.

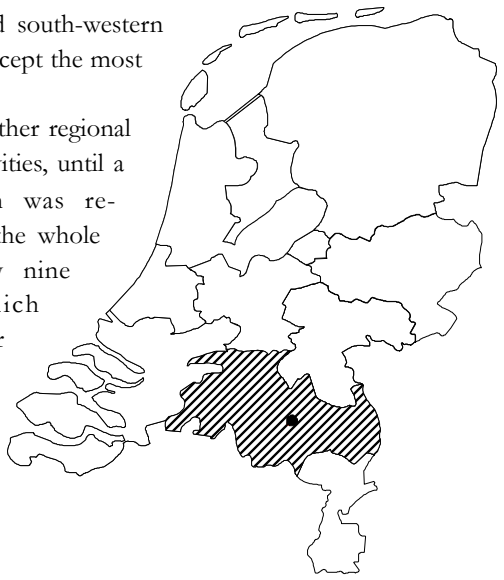

Figure 1: The current area of the Eindhoven Cancer Registry of the Comprehensive Cancer Centre South

In the Netherlands nine Comprehensive Cancer Centres, covering the entire population, are working together to improve the quality of cancer care. They exploit the regional cancer registries. In addition to the development of treatment guidelines they play an important role in the implementation of and the promotion of adherence to the guidelines. Furthermore they coordinate palliative care by providing for education and guidelines.[39]

The area covered by the population-based Eindhoven Cancer Registry, with approximately 2.4 million inhabitants in 2004, (15% of the Dutch population) is now served by 10 general hospitals at 16 locations and two large radiotherapy institutes, one in the western (Tilburg) and one in the eastern (Eindhoven) part of the region. The area does not contain a university hospital or a specialised cancer hospital. There are 6 pathology laboratories, all participating in the nationwide PALGA (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief) network, which also notifies the regional cancer registries.

The cancer registry receives lists of newly diagnosed cases on a regular basis from the pathology departments. In addition, the medical record departments of the hospitals provide lists of outpatients and hospitalised cancer patients. Following this notification, the medical records of newly diagnosed patients (and tumours) are collected, and trained registrars from the cancer registry abstract the necessary information, such as data on diagnosis, staging, and primary treatment, given or planned within 6 months of diagnosis. Data are checked for duplicate records.

Patients who live in the catchment area of the Eindhoven Cancer Registry, but are diagnosed elsewhere in the Netherlands, are regularly retrieved from all other Dutch Cancer Registries since 1989. Before this year it was done directly through manual retrievals at all the cancer centres.

Major aims of the registry are to host and facilitate studies on:

- Public health aspects, e.g. trends and clusters, scenarios.
- Quality of care: adherence to guidelines, studies of side effects and quality of life.
- Prognosis: focus on elderly and role of co-morbidity or social-economic status.

Generally, the region can be characterised by good access to medical care without financial obstacles. The distance to a hospital has always been less than 30 kilometres, and the travel time to a radiotherapy department is for most patients less than 30 minutes and for some almost one hour if they are not hampered by traffic jams. The population in the area is increasingly ageing, with an increasing proportion of elderly women (from less than 5% to more than 10%), and since 1965 a decreasing number of children (figure 2).

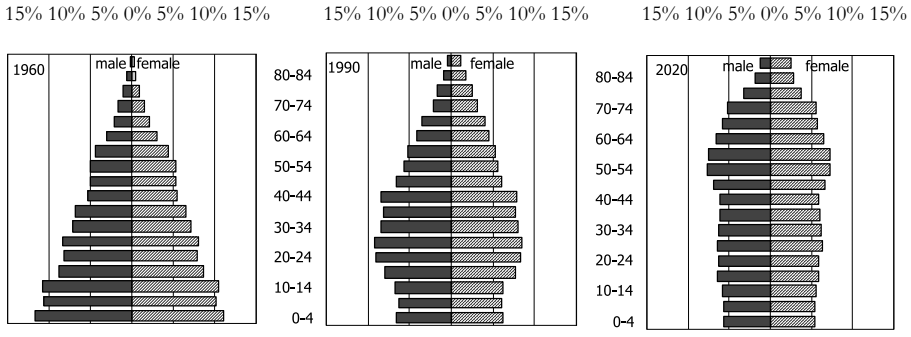

Figure 2: Age-distribution of the population in the area of the Eindhoven Cancer Registry

Histological classification and Staging

All tumours were classified based on topography and histology, according to the WHO International Classification of Diseases for Oncology (ICD-0).[40]

Stage of the tumours was categorised according to the TNM-classification International Union against Cancer (IUCC).[41]

Co-morbidity

On demand of various specialists who were increasingly worried about the age and treatability of their patients, the registry also recorded co-morbidity at diagnosis since 1993 according to a slight adaptation of the list of serious diseases drawn up by Charlson and colleagues.[42] In short, the following important conditions were recorded: chronic obstructive pulmonary diseases (COPD), cardiovascular and cerebrovascular diseases, other malignancies (excluding basal cell carcinoma of the skin), and diabetes mellitus. Furthermore, hypertension, connective tissue disease, rheumatoid arthritis, kidney, bowel and liver diseases, dementia, tuberculosis and other chronic infections were also recorded. Chapter 4.1 of this thesis contains a table of the recorded co-morbid conditions.

Radiotherapy

Primary radiotherapy was defined as radiotherapy given or planned within 6 months of date of diagnosis. Secondary radiotherapy was defined as radiotherapy given 6 months or later after diagnosis, or as radiotherapy given after a previous course of radiation for the same tumour (figure 3).

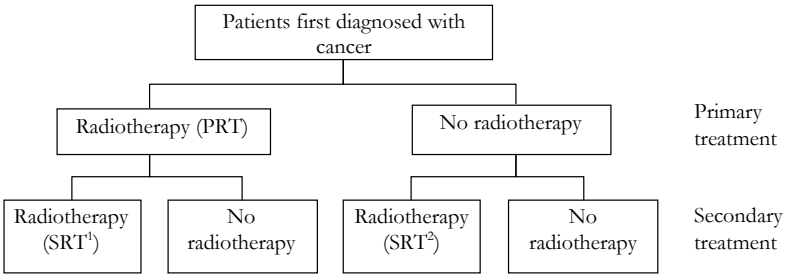

Figure 3: Flow chart of the kind of radiotherapy. PRT = primary radiotherapy, given or planned within 6 months of diagnosis; SRT^1 = secondary radiotherapy, given after a previous course of radiation for the same tumour; SRT^2 = secondary radiotherapy, given 6 months or later after diagnosis.

The area of the Eindhoven Cancer Registry is served by two large radiotherapy institutes, one in the western region as an independent facility and one in the eastern region as part of a large general hospital, each serving only community hospitals. The institutes now each treat about 2500 new (newly diagnosed cancer patients, or patients with a new episode of the disease, who were never irradiated before) patients a year and 500 to 800 patients who were irradiated before for the same tumour.

In both institutes each course of radiation (primary or secondary) is recorded with date of onset, patient characteristics and treatment protocol number, indicating the kind of treatment given. For the studies in chapter 3.1 and 3.2 data from the radiotherapy institutes were combined with data from the Eindhoven Cancer Registry.

1.3 Outline

The objectives of this thesis were to study variation in the use of radiotherapy in a variety of study designs in a large population-based setting:

- To explore trends in referral for primary radiotherapy.
- To investigate the use of secondary radiotherapy.
- To explore variations in referral for radiotherapy in relation to patients' and doctors' characteristics.

In **chapter 2.1** an overview is given of consumption of primary radiotherapy for patients with different tumour types between 1988 and 2002. Also the time trends are discussed and whether the variation decreased. Variations between hospitals in referral for primary radiotherapy are described in **chapter 2.2. Chapter 2.3** is a continuation of chapter 2.1; referral rates and trends are studied up to 2006 inclusive, and changes are discussed, with emphasis on breast and rectal cancer and differences between the two regions.

The use of secondary radiotherapy for patients with breast and rectal cancer was studied in a population-based cohort of breast cancer patients and in a cohort of rectal cancer patients. These studies are described in **chapter 3.1 and 3.2.** These are the first population-based studies to give insight in the use of secondary radiotherapy.

In **chapter 4.1** the influence of age and co-morbidity on receiving primary radiotherapy is discussed for the following tumour types: breast, rectal, lung and prostate cancer and non-Hodgkin lymphoma. **Chapter 4.2** gives a literature overview of treatment possibilities of rectal cancer since 1980, but as well as of its real management, especially in relation to age.

The results of a questionnaire among general practitioners about their knowledge of palliative radiotherapy are presented in **chapter 5.1. Chapter 5.2** describes variations in time pattern of referral for spinal cord compression.

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Chapter 2

Long-term trends

2.1

Referral rates and trends in radiotherapy as part of primary treatment of cancer in South Netherlands, 1988 - 2002

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Radiotherapy and Oncology 2006; 78: 131-137

Abstract

Background and Purpose

To study referral rates and time trends in the use of primary radiotherapy (RT).

Methods

The proportion and number of irradiated patients were calculated in a population-based setting among 58,436 cancer patients diagnosed between 1988 and 2002.

Results

The number of patients receiving RT within 6 months of diagnosis (RT6mo) increased by about 3.3% annually, the proportion of all incident cases that received RT6mo remained stable (±30%). Only 20% of elderly patients (75+) received RT6mo.

The proportion of cancer patients that received RT6mo increased markedly between 1988-92 and 1998-2002 for patients with prostate cancer (15 and 28%, respectively), rectal cancer (33 and 43%) and brain tumours (48 and 67%). The absolute number of irradiated breast cancer patients increased 30% between 1988 and 2002. Among patients with rectal cancer a shift occurred from postoperative to preoperative RT since 1995. The percentage of irradiated patients with stage I endometrial cancer decreased from 47% in 1988-92 to 15% in 1998-2002.

Conclusion

The percentage of cancer patients who received primary RT remained stable throughout 1988-2002, being consistently lower for older patients. The increased number of irradiated patients was due mainly to earlier detection and the ageing of the population. To clarify the overall percentage of patients irradiated, population-based studies on RT given after 6 months since diagnosis are warranted.

Introduction

Of all cancer patients about 50% are generally assumed to receive radiotherapy (RT) during the course of the disease.[1, 2] These percentages are normally not based on population-based studies but are nonetheless often used for decisions on the required capacity of RT equipment and personnel. The percentage usually consists of primary RT as part of an initial treatment and secondary RT in the case of recurrent disease or metastases[1, 3] without taking into account whether patients had already received primary RT. A population-based study from an adjacent RT department in Eindhoven, which belongs to the same comprehensive cancer centre, showed that 32% of the cancer patients received primary RT between 1975 and 1998.[4, 5] A study of trends in the use of RT for different tumour types, preferably by stage and age, can illustrate necessary as well as arbitrary changes and would provide an impression of adherence to guidelines, that are being developed increasingly in the Netherlands. We studied the number and proportion of cancer patients who received primary RT and analysed trends in the use of primary RT between 1988 and 2002.

Methods

The Eindhoven Cancer Registry (ECR) records data on all patients newly diagnosed with cancer in the southern part of the Netherlands with a population of approximately 2.3 million. This population-based registry covers all facilities in the region, which are: six regional pathology departments, 15 community hospitals and two large RT departments, one of which is located in the mid-western part (Tilburg) as an independent facility and the other in Eindhoven. Trained registry personnel actively collect information from the medical patients' records upon notification of newly diagnosed cases by the regional departments of pathology, haematology and radiotherapy and the national Registry of Hospital Discharge Diagnosis. Patients referred for treatment outside the area (<3%) are completely registered by the ECR. Cancer registries in the Netherlands usually cover over 95% of all cases due to the infrastructure of and good access to Dutch health care facilities, together with the multiple source notification procedures used.[6] Recorded are patient characteristics (gender, age, concomitant diseases[7]), tumour characteristics (localisation and morphology (according to the International Classification of Diseases for Oncology[8]), stage at diagnosis (according to the Tumour-Node-Metastasis (TNM) system 4th edition[9]) (which is rather complete, about 10% of all patients' stage is unknown, depending on the site of the primary tumour)), primary treatment (given or planned within 6 months of diagnosis), and date of death.

The Dr. B. Verbeeten Institute (BVI) is an independent non-academic facility, which had 3 linacs, 1 cobalt and 1 orthovolt in 1988, and 1 cobalt and 5 linacs in 2002. The number of full-time radiation oncologists increased from 5 in 1988 to 10 in 2002. The BVI provides RT for all patients diagnosed in the 8 hospitals in the western part of the Comprehensive Cancer Centre, with a growing and ageing population of approximately 1 million people,[10] where the cancer registry of the ECR has been complete since 1988.

We included all patients diagnosed with cancer (excluding carcinoma in situ, superficial bladder cancer and non-melanoma skin cancer) between 1988 and 2002 (n=58,436). We studied tumour-specific and 15-year age-specific applications of RT that is given within 6 months of diagnosis (RT6mo). Patients who are planned to receive RT after several courses of chemotherapy (so the start of radiotherapy may actually be after 6 months) are also included as having received RT6mo. Age and stage-specific trend analyses were performed for individual tumour types. For the stage specific analysis NX and MX were coded N0 and M0.

The estimated annual percentage change (EAPC) was calculated as an estimate of the trend. A regression line was fitted: i.e. $y = ax + b$, where y = rate and x = calendar year. EACP = a / b.[11]

Results

The total annual number of patients receiving RT6mo increased from 851 in 1988 to 1439 in 2002 (table 1), an EAPC of 3.3%.[11] The percentage of patients receiving RT6mo remained stable at about 30%. Thirty to forty percent of new patients between 30 and 75 years received RT6mo, and 20% of the patients older than 75 (table 1).

Table 1 - Age-specific use and share[a] of radiotherapy given within 6 months of diagnosis according to period of diagnosis in South Netherlands, 1988-2002

	1988-1992				1993-1997				1998-2002			
	No. cancer patients	No. irradiated	Irradiated (%)	Share (%)	No. cancer patients	No. irradiated	Irradiated (%)	Share (%)	No. cancer patients	No. irradiated	Irradiated (%)	Share (%)
0-44	1745	648	37.1	12.4	1862	663	35.6	11.2	1934	717	37.1	10.8
45-59	3869	1548	40	29.7	4442	1746	39.3	29.6	5164	1930	37.4	29
60-74	7041	2161	30.7	41.4	8306	2538	30.6	43	9139	2939	32.2	44.1
75+	4249	859	20.2	16.5	4981	953	19.1	16.2	5704	1073	18.8	16.1
Total	16904	5216	30.9	100	19591	5900	30.1	100	21941	6659	30.3	100

[a]Share: the proportion of irradiated patients from one age group relative to all irradiated patients in that specific period of diagnosis

Tumour-specific application of RT is shown in table 2. Patients with breast cancer (31%) and lung cancer (26% in 1988-1992, 19% in 1998-2002) form the largest portion of all irradiated patients.

The proportion of irradiated patients increased among patients with rectal tumours (33 to 43%), laryngeal tumours (73 to 88%), prostate cancer (15 to 29%), tumours of the central nervous system (49 to 67%), and Hodgkin's disease (39 to 62%). Most other tumour types showed a decrease.

Table 2 - Cancer-specific use and share[a] of radiotherapy given within 6 months of diagnosis according to cancer site and period of diagnosis in South Netherlands, 1988-2002

	1988-1992				1993-1997				1998-2002			
	No. Cancer patients	No. irradiated	Irradiated (%)	Share (%)	No. Cancer patients	No. irradiated	Irradiated (%)	Share (%)	No. Cancer patients	No. irradiated	Irradiated (%)	Share (%)
Head and neck												
Oral cavity/ pharynx	366	169	46.2	3.2	407	194	47.7	3.3	445	245	55.1	3.7
Larynx	222	162	73	3.1	222	175	78.8	3	233	206	88.4	3.1
Rectum	832	279	33.5	5.3	946	320	33.8	5.4	1058	454	42.9	6.8
Lung	2783	1344	48.3	25.8	2940	1383	47	23.4	3119	1285	41.2	19.3
Breast	2660	1589	59.7	30.5	3138	1833	58.4	31.1	3692	2047	55.4	30.7
Gynaecological												
Cervix	220	123	55.9	2.4	195	85	43.6	1.4	182	90	49.5	1.4
Corpus uteri	327	164	50.2	3.1	382	146	38.2	2.5	470	109	23.2	1.6
Ovary	338	55	16.3	1.1	418	10	2.4	0.2	397	2	0.5	0
Urological												
Prostate	1266	192	15.2	3.7	1841	379	20.6	6.4	2240	643	28.7	9.7
Bladder	352	186	52.8	3.6	377	184	48.8	3.1	448	177	39.5	2.7
Testis	86	28	32.6	0.5	146	51	34.9	0.9	157	69	43.9	1
Lymphomas												
Hodgkin's disease	103	40	38.8	0.8	107	59	55.1	1	113	70	61.9	1.1
Non-Hodgkin	575	111	19.3	2.1	745	154	20.7	2.6	741	206	27.8	3.1
CNS[b]	231	112	48.5	2.1	290	174	60	2.9	295	198	67.1	3
Myeloma	170	41	24.1	0.8	198	51	25.8	0.9	202	59	29.2	0.9
Oesophagus	184	80	43.5	1.5	250	102	40.8	1.7	375	140	37.3	2.1
Soft tissue	242	43	17.8	0.8	251	47	18.7	0.8	273	47	17.2	0.7
Unknown primary	824	144	17.5	2.8	892	208	23.3	3.5	1033	192	18.6	2.9
Other sites[c]	5123	354	6.9	6.8	5846	345	5.9	5.8	6468	420	6.5	6.3
Total	16904	5216	30.9	100	19591	5900	30.1	100	21941	6659	30.3	100

Excluded carcinoma in situ, superficial bladder cancer and non-melanoma skin cancer

[a]Share: the proportion of one irradiated tumour type relative to all tumours in that specific period of diagnosis

[b]CNS=Central Nervous System

[c]All other invasive tumours except non-melanoma skin cancer

The proportion irradiated patients with non-small cell *lung cancer* decreased from 48 to 41% (figure 1), which can be attributed mostly to patients with a non-localised (stage III and IV) tumour, 57% of all patients with non-small cell lung cancer. Forty percent of the patients with limited small cell lung cancer younger than 70 received RT in 2002 in contrast to 26% in 1988.

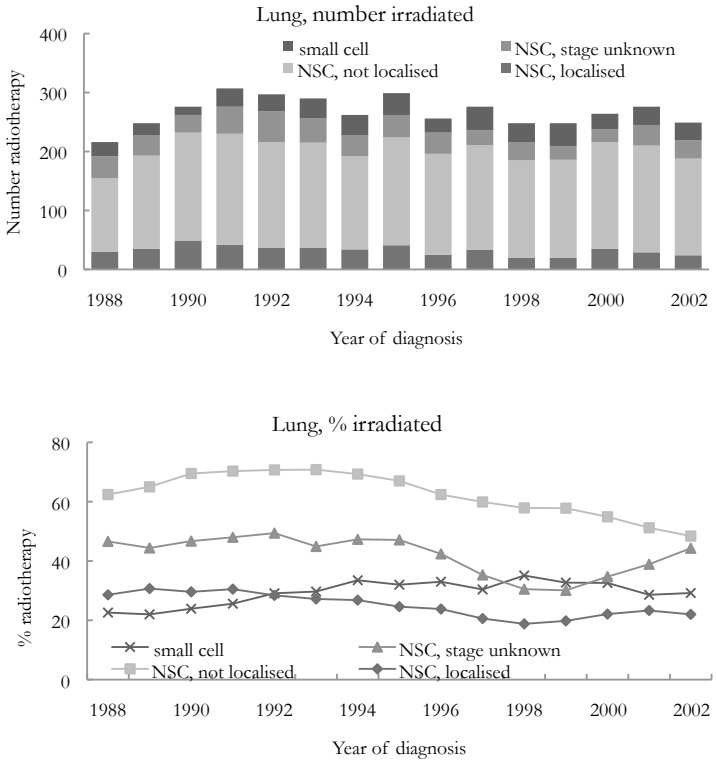

Figure 1: Number and percentage of patients with lung cancer receiving radiotherapy according to stage and year of diagnosis in South Netherlands, 1988-2002
Non-small cell (NSC) localised: T1-2 N0/X M0/X; T1-2/X N1 M0/X
Non-small cell not localised: T1-2/X N2 M0/X; T3 N0-2/X M0/X; T4 N0-3/X M0/X T1-4/X N3 M0/X; T1-4/X N0-3/X M1

The number of irradiated patients with *prostate cancer* increased from 29 in 1988 to 171 in 2002, the proportion from 15 to 32%**.** The increase was most striking for those with a localised tumour (table 3).

The total number of irradiated patients with *breast cancer* was approximately 30% higher in 1992 compared with preceding years (figure 2), mainly due to patients between 50 and 69 years with stage I or II. The percentage of patients aged 70 and older receiving RT was approximately 20% lower compared to younger patients, for all stages of the disease.

The number of irradiated patients with *rectal cancer* showed a slight increase, the proportion was stable until 2000 (table 2). From 1997 onwards postoperative RT was partly replaced by preoperative RT, and from 2001 it was almost entirely preoperative (figure 3).

The percentage of irradiated patients with *endometrial cancer* decreased from 50% in 1988-1992 to 23% in 1998-2002 (table 2), mainly due to stage I patients. The proportion of patients younger than 70 years with *bladder cancer* who received RT decreased more (55 to 31%) than the proportion of older patients (53 to 46%).

The proportion and the number of irradiated patients with tumours of the *central nervous system* increased (figure 4), mainly because of the increased irradiation of patients older than 55 years with high grade astrocytoma.

The proportion irradiated patients with *Hodgkin's disease* increased until 1999 to 70%, and then decreased to 58% in 2002. The proportion irradiated patients with *non-Hodgkin's* disease increased from 17% to 27% (table 3, figure 4).

Table 3 - Radiotherapy consumption in prostate cancer according to stage and period of diagnosis in South Netherlands, 1988-2002

	1988-1992			1993-1997			1998-2002		
	No. cancer patients	No. irra-diated	Irra-diated (%)	No. cancer patients	No. irra-diated	Irra-diated (%)	No. cancer patients	No. irra-diated	Irra-diated (%)
Localised[a]	658	124	18.8	1117	267	23.9	1520	488	32.1
Locally advanced[b]	94	24	25.5	193	60	31.1	264	101	38.3
Metastasised[c]	359	29	8.1	366	36	9.8	347	41	11.8
Unknown	155	15	9.7	165	16	9.7	109	13	11.9
All stages	1266	192	15.2	1841	379	20.6	2240	643	28.7

[a] T1-2 N0/X M0/X
[b] T3-4 N0/X M0/X
[c] T1-4/X pN1 M0/X; T1-4/X pN0-1 M1

Discussion

The total number of cancer patients increased substantially during 1988-2002,[10] as a result of a growing and ageing population. The number of patients who received RT6mo in the western part of the ECR also increased (3.3% annually), but the proportion remained stable: about 30% of cancer patients received radiotherapy. In the eastern part of the ECR a slightly higher percentage of 32% was found between 1975 and 1998,[5] mainly due to a higher proportion irradiated patients with breast and prostate cancer. A report estimating required RT equipment assumed that 47% of the cancer patients received RT in 1995 and that this would increase to 50% in 2010.[12] This report, and also other reports[1-3] did not separate RT6mo from RT given later during the course of the disease and the numbers were not obtained from population-based studies but were rather expert-opinions.

Earlier, we estimated that 45% of all patients received irradiation, including 32% RT6mo, 5% RT for the first time for relapsed disease or metastases, and 40% after an earlier irradiation.[4]

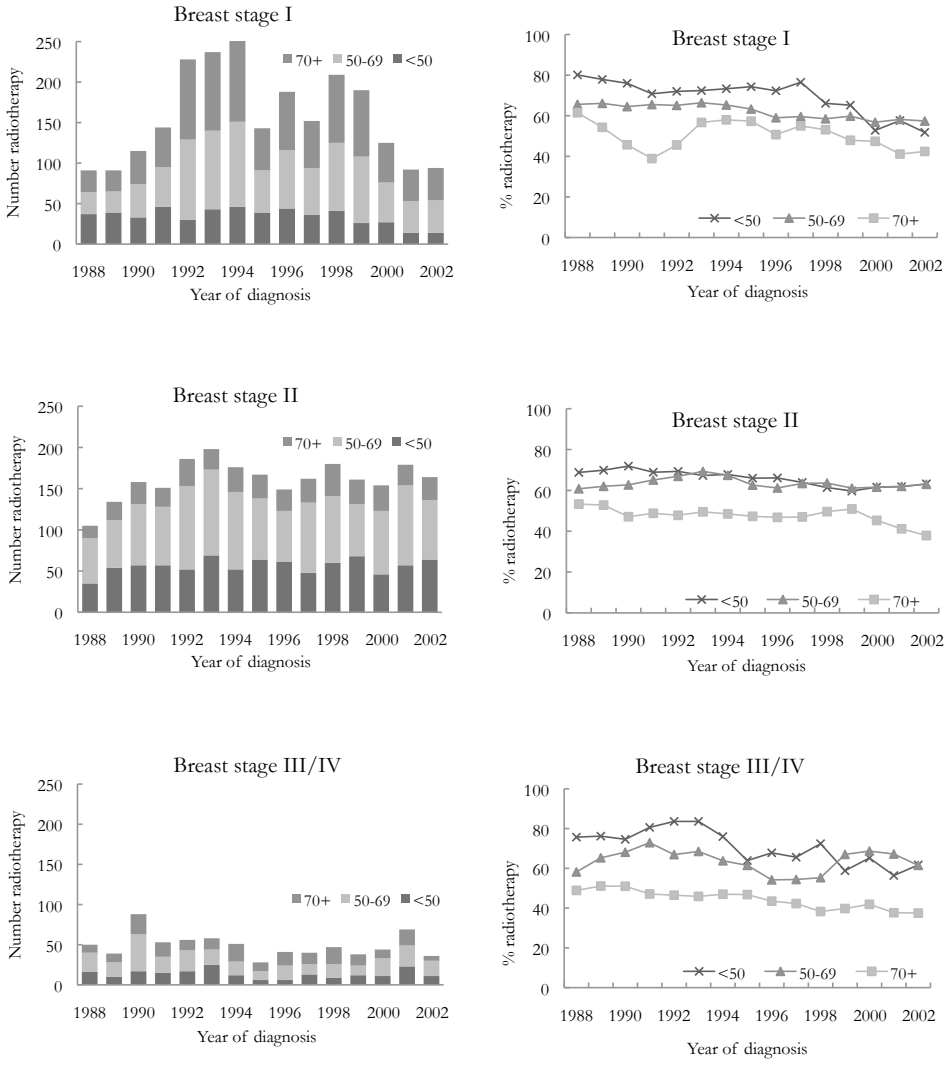

Figure 2: Number and percentage of patients with breast cancer receiving radiotherapy according to year of diagnosis, age and stage in South Netherlands, 1988-2002
Stage I: T1 N0 M0/X
Stage II: T2 N0-1 M0/X; T1 N1 M0/X; T3 N0 M0/X
Stage III: T1-2 N2 M0/X; T3 N1-2 M0/X; T4 N0-3/X M0/X; T1-4 N3 M0/X
Stage IV: T1-4/X N0-3/X M1

In Australia, the proportion of cancer patients who receive RT at some point of their illness was calculated to be 52%.[13]

Elderly patients (>75) received less RT, the proportion was 10-20% lower than among younger patients (table 1). Other authors concluded that use of adjuvant RT decreases more with age than can be explained by an age-associated decline in functional status observed in the general population.[14] The general attitude of doctors is influenced by the belief that tolerance to treatment might be compromised in older patients or that the course of cancer might be less aggressive in this age group.[15]

The BVI participates extensively in trials that compare different radiation doses or fields, sometimes in combination with chemotherapy. Because randomisation takes place after referral, these trials barely influence the percentage of patients irradiated. However, two trials focused on the additional value of RT: the TME-rectum trial and the Portec-study (endometrial cancer) (described later).[16, 17]

The introduction of better diagnostic possibilities improved the selection for surgical resection among patients with localised *non-small cell lung cancer*, also for older patients.[18] For non-localised tumours a combination of chemotherapy and RT replaced the RT alone.[19] The decreased percentage of irradiated patients accompanied an increased use of chemotherapy.[18] We found an increase in the percentage of irradiated patients with *small cell lung cancer,* especially patients younger than 70 years with limited disease. The real level of RT may be underestimated because of a time delay: patients with small cell lung cancer receive chemotherapy followed by consolidation RT,[20] often later than 6 months after diagnosis. In the early years these patients were not always registered as having received RT. The overall percentage of patients with lung cancer receiving primary RT6mo (45.4%) corresponds with that estimated by an evidence-based approach (45.9% ± 4.3%), although it differed by stage, probably due to different indications for RT in North America.[21]

The total number of patients with *prostate cancer* increased markedly because of the growing number of older men in the population, and because the wide-spread use of the PSA-test since 1994.[22] The treatment of localised prostate cancer largely depends on the preference of the urologist.[23] Although alternative treatments are available, such as radical prostatectomy or watchful waiting, a large increase was observed in the proportion irradiated patients with a localised tumour.[24] The percentage of 30% irradiated patients in the last period corresponds with the evidence-based estimate of 32.2% ± 3.8% from the model by Foroudi and colleagues.[25] In North America, where incidence rates are much higher, the share of irradiated patients is also higher than in our study.[10, 26]

The absolute number of patients with *breast cancer* increased because of the introduction of mass screening in 1991. Also the number of patients who received breast-conserving therapy including RT increased.[27] The slight decrease in percentage irradiated patients younger than 70 years with stage I and II in the nineties indicates that fewer patients with a relatively small tumour received breast-conserving therapy.[27-29] This will have the same result in terms of disease-free survival and survival as mastectomy.[30, 31] Referring specialists apparently had different ideas about the best therapy.[32]

Also in other countries treatment of small breast tumours was (too) often amputation, or breast-conserving surgery without RT.[33, 34] Patients aged 70 years and older were less often treated according to therapy guidelines.[14, 35, 36] The overall percentage of 54-60% irradiated patients is similar to the evidence-based result of 57.3% ± 4.7% in initial treatment.[37]

The standard treatment for patients with *rectal cancer* was surgery followed by RT until a reduction was seen in the local recurrence rate for patients who received preoperative RT.[38, 39] From 1996 to 1999 most patients received preoperative RT within the framework of the TME trial (total mesorectal resection with or without preoperative RT).[16] The proportion irradiated patients remained stable because of the high participation in this trial. In 2002 the percentage of patients receiving RT had increased from 40% to 65%, almost all preoperative (figure 3). An evidence-based estimation from 2003 showed that 69.6% ± 0.9% of rectal cancer cases would require RT in their initial treatment. These numbers are based on the North American management of rectal carcinoma, which consists of postoperative RT in most centres.[40] We found a much lower percentage of postoperative irradiated patients (35%).

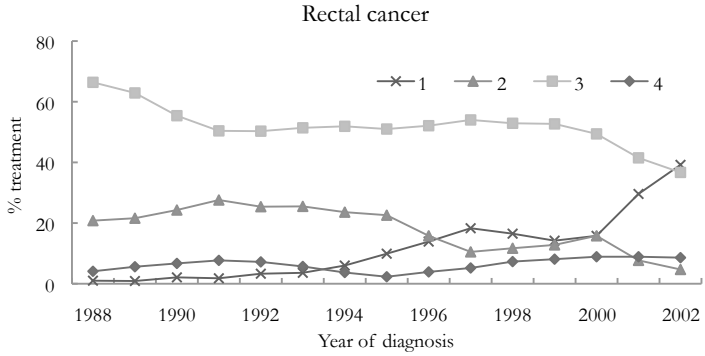

Figure 3: Treatment (%) of rectal cancer according to year of diagnosis in South Netherlands, 1988-2002
1=preoperative radiotherapy, 2=postoperative radiotherapy, 3=only surgery,
4=only radiotherapy (patients with other or unknown therapy were excluded)

The BVI actively participated in the Portec-Trial that studied the value of radiotherapy for patients with stage I *endometrial carcinoma***.** Postoperative RT was controversial for this tumour.[41] Patients were randomised to receive pelvic RT or no further treatment after total abdominal hysterectomy. Consequently the percentage irradiated patients with stage I decreased. An even further decrease was seen after 1999, especially for patients younger than 60, but also for older patients, according to the guidelines which were developed from the results of the Portec-Trial,[17] but also because more patients had undergone lymph node dissection.[42] The optimal RT utilisation at some point of the illness in Australia was 34% if pelvic lymph node dissection was widely practised, otherwise 58%.[43]

Until the early nineties patients with *bladder cancer* received often RT before a cystectomy. Since then, more patients were operated, but without RT.

For patients with a high-grade *astrocytoma* the median survival increases after postoperative RT.[44] There is no consensus on the treatment strategy for patients with a low-grade glioma. Postoperative RT appears to improve the progression-free survival, but not overall survival.[45]

Patients with *Hodgkin's disease* received RT alone or in combination with chemotherapy.[46] The low percentage of patients irradiated found at the end of the eighties and early nineties (figure 4) is probably a registration artefact: RT given in combination therapy after chemotherapy was not always coded as a primary treatment in the early years of the cancer registry. The proportion of irradiated patients we found in the period 1998-2002 (70%) was comparable to that from an evidence-based estimation in Australia (75%).[47]

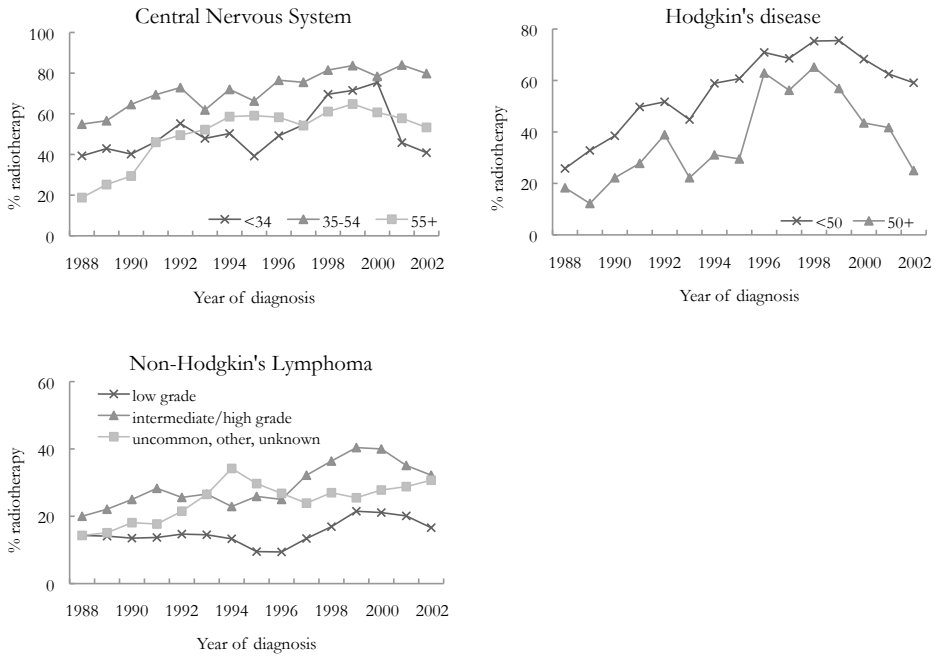

Figure 4: Percentage of patients who received radiotherapy: Central Nervous System and Hodgkin's disease according to year of diagnosis and age; non-Hodgkin's lymphoma according to year of diagnosis and stage in South Netherlands, 1988-2002

Since 1997 patients with a low-grade *non-Hodgkin's lymphoma* receive a fraction of 4 Gray at the affected localisation.[48] The increase in the proportion of irradiated patients with an intermediate/high grade non-Hodgkin's lymphoma is probably a registration artefact as well, as is explained above.[49] According to an evidence-based estimation in 2004 the proportion of patients in Australia that should receive RT at some point in their treatment, was calculated 64%, which was much higher than our findings of only RT6mo (28%).[47]

Conclusion

Although the number of cancer patients receiving RT6mo increased markedly in the last 15 years, the overall percentage, which was lower for the elderly, remained stable, despite an increase in the number of linacs and staff as well as screening campaigns. Changing indications often based on results of randomised clinical trials went in both directions.

To clarify the overall percentage of patients irradiated, population-based studies on secondary RT should also be performed.

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2.2

Hospital variation in referral for primary radiotherapy in South Netherlands, 1988-1999

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Abstract

We assessed whether referral for primary radiotherapy varied according to hospital size in a region with 1 million inhabitants served by community hospitals. We studied 20,178 patients diagnosed with breast, non-small cell lung, prostate, rectal, or endometrial cancer between 1988 and 1999. We used logistic regression analysis, adjusted for age, stage and period of diagnosis. Medium-sized and small hospitals referred breast cancer patients more often (OR=2.2, 95%CI=2.0-2.5, OR=1.2, 95%CI=1.1-1.4, respectively) and patients with prostate cancer less often (OR=0.7 (0.5-0.8) and 0.7 (0.6-0.9), respectively). Referral rates for patients with non-small cell lung and rectal cancer showed minor differences according to hospital size, referral for endometrial cancer was somewhat higher for patients from medium-sized hospitals (OR=1.5 (1.0-2.1)). Time trends in variation were shown, but differences according to hospital size only decreased over time for rectal cancer. Despite multidisciplinary oncology meetings and treatment guidelines there were large variations in rates of referral for radiotherapy.

Introduction

Of all cancer patients 50-60% are assumed to receive radiotherapy (RT).[1-3] These numbers are often used in decision-making, for example to calculate required capacity of RT equipment. According to a population-based study from the Eastern part of the Eindhoven Cancer Registry (ECR) approximately 30% of all cancer patients received primary RT between 1975 and 1998.[4, 5] We found the same percentages for the western part of the ECR (data not shown). Little is known about the inter-hospital variation in referral patterns. Our regional radiotherapy department operates in a region covered by the Comprehensive Cancer Centre South, which promotes adherence to (and sometimes development of) guidelines. The area includes a population-based cancer registry and is served by community hospitals only. This allows us to study the variation in rates of referral for a regional radiotherapy department in a population-based setting.

Methods

The ECR records data on all patients newly diagnosed with cancer in the southern part of the Netherlands; it covers a population of approximately 2.3 million. This population-based registry includes six pathology departments, 15 community hospitals (no university hospital) and two RT departments, one of which is located in the western part (Tilburg) as an independent facility. Data on patient characteristics (age, gender, concomitant diseases), tumour characteristics (localisation, morphology, stage at diagnosis) and treatment (planned within 6 months of diagnosis) is recorded by trained registry personnel, usually between 6 and 18 months after diagnosis. Despite the lack of access to death certificates, the infrastructure of and good access to Dutch health care facilities, together with the multiple source notification procedures used, cancer registries in the Netherlands typically cover over 95% of cases.[6] The Dr. B. Verbeeten Institute (BVI) offers RT in the western part of the region. Within the referral area the number of referring hospitals decreased due to mergers from 9 to 7 between 1988 and 1999, but the original locations (units of patient care) were retained. A subdivision was made into large (more than 500 beds, n=2), medium-sized (350-500 beds, n=3) and small hospitals (less than 350 beds, n=4). Physicians' training facilities were present in both large and some of the medium-sized hospitals. Treatment guidelines for most tumour types were available. In all hospitals cancer patients were presented on multidisciplinary oncology meetings, in the presence of a radiation oncologist to discuss treatment policy. We included all patients with cancer of the breast, prostate, rectal and endometrial and non-small cell lung cancer diagnosed between 1988 and 1999 (n=20,178). We studied both the individual hospital and the hospital size. In stage-specific[7] analysis of breast cancer NX and MX were coded N0 and M0, respectively. Differences in distribution were tested with the chi-square test. Logistic regression analysis was used to estimate the effect of hospital size on the referral for RT, adjusted for age, stage and period of diagnosis.

Results

Forty-five percent of patients in the study received primary RT (i.e. within 6 months of diagnosis). The lowest percentage (42%) of cancer patients was referred for RT in the large hospitals (medium: 43%, small: 51%, p<0.0001). Variation in stage existed between the hospitals for most tumour types. Regardless of hospital size, referral for RT was lower for patients aged 70+ compared to those below 70, except for non-small cell lung cancer (table 1). This was also demonstrated by the multivariate analysis (table 2). The largest effect was observed for breast cancer patients, the odds for receiving RT were 0.3 for patients aged 70+ compared to those diagnosed before age 70 (95%CI=0.3-0.4).

Table 1 - Total number of cancer patients and referral rates (%) for primary radiotherapy according to hospital size[a] and age in South Netherlands, 1988-1999

Tumour type	Age	Hospital size		
		Large	Medium	Small
Breast cancer				
No. patients		2211	3023	2336
% irradiated	< 70	57	63	75
	≥ 70	35	35	50
NSCLC[b]				
No. patients		2830	2456	549
% irradiated	< 70	45	48	45
	≥ 70	44	45	48
Prostate cancer				
No. patients		1260	1583	902
% irradiated	< 70	32	28	25
	≥ 70	21	15	18
Rectal cancer				
No. patients		616	869	658
% irradiated	< 70	40	44	46
	≥ 70	25	23	28
Endometrial cancer				
No. patients		286	341	258
% irradiated	< 70	38	43	45
	≥ 70	33	37	49
Total				
No. patients		7203	8272	4703
% irradiated	< 70	47	51	60
	≥ 70	34	30	35

[a]large = >500 beds, n=2; medium = 350-500 beds, n=3; small = <350 beds, n=4; [b]NSCLC = non-small cell lung cancer

Patients with *breast cancer* from large hospitals were referred for RT less often (42%, medium-sized 43% and small 50%, p<0.0001) (table 1). When adjusted for age, stage and period of diagnosis, the chance to receive RT was higher for patients referred by specialists in the medium-sized (OR=2.2, 95%CI=2.0-2.5) and the small hospitals (OR=1.2, 1.1-1.4).

Especially patients with stage I and II breast cancer from the small hospitals received RT more often (70-80% compared to 50-60% from the medium-sized and large hospitals, p<0.0001).

Specialists in the large and medium-sized hospitals referred most of the patients with *non-small cell lung cancer* for RT. The referral of non-small cell lung cancer patients decreased from 50% in 1988 to 36% in 1999 with only small variations according to hospital size or individual hospital.

Table 2 - Chance to receive primary radiotherapy for different tumour types according to hospital size[a] adjusted for age, stage[b] and period of diagnosis in South Netherlands, 1988-1999

	Breast cancer		NSC lung cancer[c]		Prostate cancer		Rectal cancer		Endometrial cancer	
	OR[d]	95%CI[e]	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Hospital type										
Large*	1		1		1		1		1	
Medium sized	2.2	2.0-2.5	0.9	0.7-1.1	0.7	0.5-0.8	1.2	0.9-1.6	1.5	1.0-2.1
Small	1.2	1.1-1.4	1.2	1.0-1.3	0.7	0.6-0.9	0.9	0.7-1.2	1.1	0.8-1.6
Age										
<70*	1		1		1		1		1	
≥70	0.3	0.3-0.4	1	0.9-1.2	0.6	0.5-0.7	0.4	0.3-0.5	0.9	0.7-1.2
Stage										
I*	1		1		1		1		1	
II	1	0.9-1.1	3	2.6-3.4	1.3	1.1-1.6	4.4	3.3-5.8	3.2	1.9-5.5
III	1.8	1.5-2.1			1.6	1.2-2.1	8.7	6.5-11.8	4.2	2.4-7.3
IV	0.2	0.1-0.2			0.1	0.0-0.1	1.2	0.8-1.7	0.5	0.2-1.3
Unknown	0.3	0.2-0.4	1.5	1.3-1.8	0.5	0.3-0.7	4.8	3.4-6.9	0.5	0.2-1.5
Period of diagnosis										
1988-1991*	1		1		1		1		1	
1992-1995	1	0.9-1.1	1	0.9-1.2	1	0.8-1.3	1	0.7-1.2	0.7	0.5-1.0
1996-1999	0.8	0.7-0.9	0.6	0.5-0.7	1.3	1.0-1.6	0.9	0.7-1.2	0.5	0.4-0.7

[a]large=>500 beds, n=2, medium sized=350-500 beds, n=3, small=<350 beds, n=4
[b]NSC lung cancer: I=localised, II=non-localised; [c]NCS = non-small cell; [d]OR = Odds ratio
[e]CI=Confidence Interval; *reference category

Specialists in the large hospitals referred 25% of patients with *prostate cancer* for RT (medium 19% and small 20%, p<0.0001). The chance of RT after adjustment was significantly lower for patients from small and medium-sized hospitals (OR=0.7, 95%CI= 0.5-0.8, OR=0.7, 95%CI=0.6-0.9, respectively).

For *rectal cancer* the referral rates for RT were approximately 35% regardless of hospital size.

Patients with *endometrial cancer* were referred more often by specialists in the medium-sized or small hospitals (41% and 47%, respectively), compared to the large hospitals (36%, p=0.06). According to multivariate analysis the chance that patients from medium-sized hospitals would receive RT was significantly higher (OR=1.5, 95%CI=1.0-2.1) (table 2).

The variation in referral between individual hospitals was large for patients with breast cancer (mean 58%, range 44-71%), prostate cancer (mean 22%, range 12-33%), rectal cancer (mean 36%, range 28-48%) and endometrial cancer (mean 42%, range 29-63%). For non-small cell lung cancer the referral rate ranged from 32-49% (mean 46%), with an outlier (65%) for 1 small hospital with only a few patients (figure 1).

The time trend in variation according to hospital size is shown in figure 2. The referral rates converged for rectal cancer. The differences remained stable for patients with breast, non-small cell lung and endometrial cancer, and the variations became larger for prostate cancer.

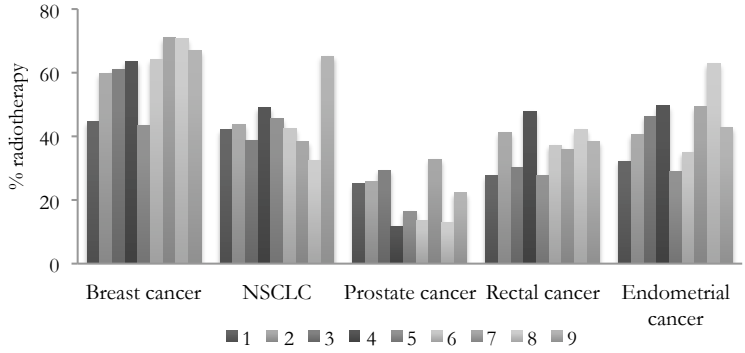

Figure 1: Referral for primary radiotherapy (%) according to tumour type and hospital in South Netherlands, 1988-1999 (NSCLC = non-small cell lung cancer)
1,2: large hospitals; 3,4,5: medium-sized hospitals; 6,7,8,9: small hospitals

Discussion

The rate of referral for primary RT in the study region (the western part of the ECR) was 30% between 1988 and 1999 for all cancer patients (data not shown), and 45% for the 5 tumour types studied, which is very similar to that found for the eastern part of the ECR.[4, 5] We found variations in referral rates for RT between the different hospitals. Variations in referral rates might be explained by the preference of specialists with regard to treatment chosen, sometimes despite treatment guidelines. Some variation can be explained by the choice of the patient. Although a variation in stage was seen for most tumour types between the hospitals, this cannot explain the variation in referral rates for RT because we corrected for this in the multivariate analysis (table 2).

The slight increase in rates of referral for RT for *breast cancer* in 1992-1994 can be explained by the introduction of mass screening in 1992. For most small breast cancers conservative surgery with RT was established as the standard treatment because it gave the same results in terms of disease-free survival and overall survival as mastectomy.[8-10]

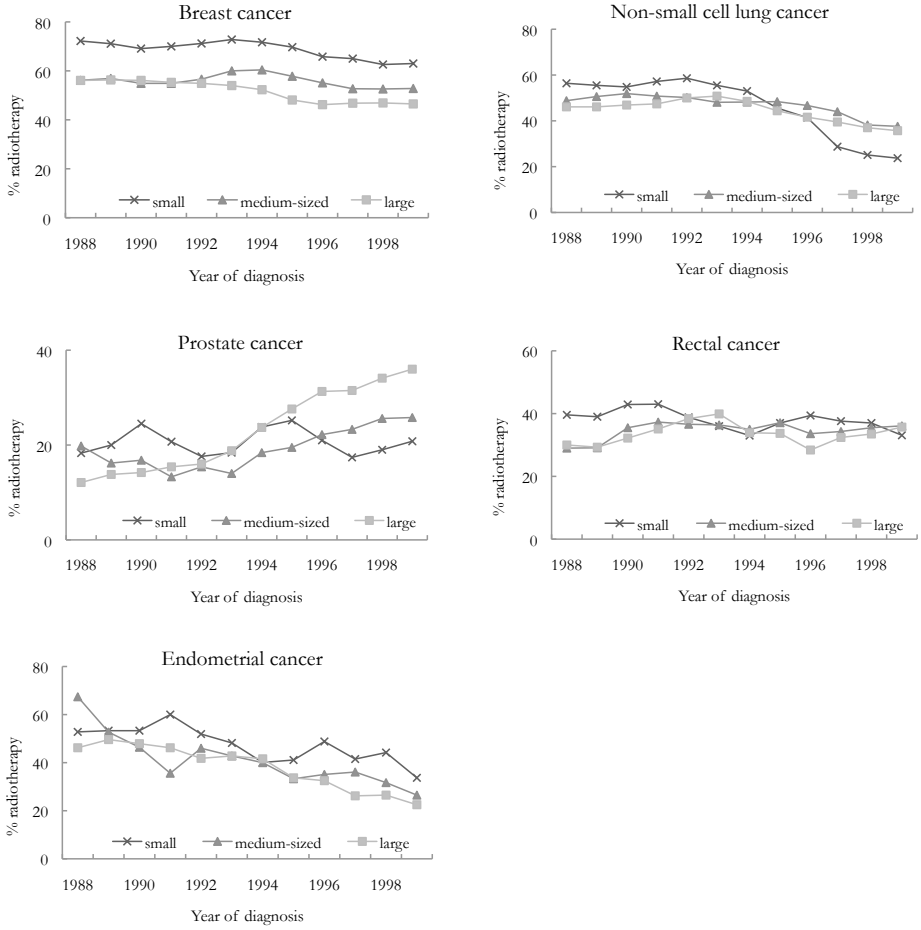

Figure 2: Time trends for variation in referral for primary radiotherapy (%) according to tumour type and hospital size in South Netherlands, 1988-1999

Nevertheless we found a large difference in the referral rates for RT (which is an important indicator of the percentage of patients undergoing conservative surgery[11]), between hospitals. The small hospitals, with the lowest caseload, had the highest percentage referrals. In these hospitals a larger proportion of patients was presented at the multidisciplinary oncology meetings. Probably because of the fact that less expertise on cancer treatment was available these meetings had more influence on the treatment policy in these hospitals. Other authors found the opposite: according to Moritz and colleagues surgeons with a higher caseload had a lower mastectomy rate,[12] and Nattinger and colleagues noted that larger hospitals were more likely to perform breast-conserving surgery compared to smaller hospitals.[13]

In our region the choice between conservative treatment and mastectomy in the larger hospitals was influenced markedly by the personal experience and practice of the individual surgeon, and to a lesser extent by multidisciplinary recommendations.

The decreasing rate of referral for RT for patients with *non-small cell lung cancer* was seen in all hospitals, probably as a result of increased use of chemotherapy.[14]

Since 1994 the PSA-test has been used for detection of *prostate cancer*. More patients with a localised tumour were referred for RT from that time.[15] The large variation in referral rates may be related to the preference of the urologist for different treatment modalities. This variation in the management of localised prostate cancer (prostatectomy, RT or watchful waiting) exists world-wide.[16-19]

From 1996 most patients with *rectal cancer* were treated with preoperative instead of postoperative RT within the framework of the TME trial (Total Mesorectal Resection with or without preoperative RT).[20] Before 1994 referral rates converged, then they diverged to lower referral rates for the large and higher referral rates for the small hospitals. Since 1996 the referral rates have converged again.

Variation in referral of patients with *endometrial cancer* stage I, similar variations were also found in the south-eastern part of the Netherlands,[21] can be explained by the lack of conclusive evidence for postoperative RT, which was therefore applied depending on the individual gynaecologists and the individual oncology meetings. When the results of the Portec trial[22] became available in 1997, the decreasing trend was interrupted for patients aged 70+, but differences according to hospital sizes remained.

For each of the investigated tumours we found variations in the rates of referral for RT according to hospital size. However, we did not find that the highest referral rates were always from one particular hospital size. For one tumour the small hospitals referred most patients, for another tumour large hospitals referred the most. After a change in treatment policy the same trend in referral for RT was found for all three hospital sizes, but for most tumour types the variations in referral rates remained.

Conclusion

Despite the existence of guidelines and multidisciplinary oncology meetings during which the treatment policy for cancer patients is discussed, large variations, with a slight convergence in later years, were found for the referral rates for RT.

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2.3

Population-based study of trends and variations in radiotherapy as part of primary treatment of cancer in South Netherlands between 1988 and 2006: emphasis on breast and rectal cancer

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Abstract

Purpose

To explore still existing variations in use of primary radiotherapy (RT) in a region with two RT departments with adjacent referral areas.

Methods and Materials

We calculated the proportion of all 147,588 newly diagnosed cancer patients between 1988 and 2006 in the south of the Netherlands receiving primary radiotherapy, according to referral to the RT departments.

Results

The number of newly diagnosed patients receiving primary RT increased from 1668 in 1988 to 2971 in 2006, the proportion remaining more or less stable (±30%). Only 20% of elderly patients (75+) received primary RT, slightly more in the eastern area.

Over time, more irradiation was administered to patients with prostate and rectal cancer, less to patients with lung and bladder cancer or Hodgkin's lymphoma and recently more to patients with cervix or endometrial cancer. The proportion remained more or less unchanged for patients with most other tumour types and became slightly higher in the eastern region. Patients with breast or rectal cancer from the eastern part of the region were significantly more likely to receive primary RT (OR=1.4, 95%CI=1.4-1.5, OR=1.4, 95%CI=1.3-1.6, respectively).

Conclusions

During 1988-2006 the number of irradiated patients increased substantially, while the proportion remained stable. Large variations were found in referral rates for RT, especially in later years, between the eastern and the western parts of the region, each with their own RT departments and referring hospitals.

Introduction

Of all patients with cancer about 50% are generally assumed to receive radiotherapy (RT) during the course of their disease.[1] This percentage is, in a way, experts' opinion but is nonetheless often used for decisions on the current and future required capacity of RT equipment and personnel. It usually consists of primary RT as part of an initial treatment and secondary RT for recurrent disease or metastases,[1, 2] irrespective of whether patients had already received primary RT. Population-based studies from our region showed that a constant percentage (about 30%) of all cancer patients received primary RT.[3-5] Furthermore, 67% of all patients with breast cancer and 45% of all patients with rectal cancer received RT (primary or secondary) in the first 5 years after diagnosis.[6, 7]

Between 1988 and 1999 referral for primary RT per hospital varied substantially in our region,[8] as well as in other parts of the Netherlands and in the USA, especially for patients with breast cancer.[9, 10] Feedback among referring specialists during 2004-05 led to many discussions, encouraging us to continue our earlier studies on variations in the use of primary RT for different tumour types. This can serve as a means to detect improved adherence to guidelines, increasingly available at a national level in the Netherlands.

We estimated the proportion of all cancer patients who received primary RT and analysed more in-depth trends and variations in the use of primary RT for patients with primary breast and rectal cancer newly diagnosed between 1988 and 2006.

Methods and Materials

Data were derived from the Eindhoven Cancer Registry (ECR), which contains data on all patients newly diagnosed with cancer since 1955. The registry covers a large part of South Netherlands with approximately 2.4 million inhabitants in 2004. The medical infrastructure consists of six Pathology Departments, 10 general hospitals (there were 20 hospitals 25 years ago) and two large RT departments, one in the west as an independent facility (Tilburg) (currently with 7 megavoltage units) and one in the east (Eindhoven) as part of a large general hospital (now with 6 units). Most patients live within a travelling range of 30 minutes to one hour from the RT department. Trained registry personnel from the ECR actively collect data from the hospital charts after notification of newly diagnosed cases by the regional Pathology and Haematology Laboratories and Radiotherapy Departments as well as the national Registry of Hospital Discharge Diagnoses. Patients referred for treatment outside the area (<3%) are completely registered in the ECR, but often a few years later. Cancer registries in the Netherlands usually comprise over 95% of all cases due to the infrastructure of and good access to Dutch health care facilities, together with the multiple notification procedures used.[11] Recorded are patient characteristics (gender, age, concomitant diseases[12]), tumour characteristics (localisation and morphology (according to the International Classification of Diseases for Oncology[13]), stage at diagnosis (according to the Tumour-Node-Metastasis (TNM) system[14]) (unknown for only 10% of all patients, depending on the site of the primary tumour)) and primary treatment.

The cancer registries are part of the Comprehensive Cancer Centres which have a largely coordinating role, enhancing communication among the various regional tumour study groups by publishing studies of adherence to guidelines.

We included all patients (n=147,588) diagnosed with cancer between 1988 and 2006 (excluding carcinoma in situ, superficial bladder and non-melanoma skin cancer). We studied tumour-specific and 15-year age-specific use of primary radiotherapy (RT) given within 6 months of diagnosis for the total group of patients, and for the western and eastern regions separately. Patients who were scheduled to receive RT after several courses of chemotherapy (sometimes after 6 months) are also included in the analyses. RT given within 6 months for metastases, if present at diagnosis, was not included, in contrast to previous studies.[4, 5]

For breast and rectal cancer patients we studied in more detail primary RT according to stage (only for breast cancer) and age and also separately for the populations from the eastern and the western regions. The changes in time of the percentage irradiated patients with breast and rectal carcinoma per individual hospital were also evaluated.

For stage classification of breast cancer the pathological TNM was used after breast-conserving surgery, breast amputation or other surgery; otherwise the clinical TNM was used, NX and MX being coded N0 and M0.

We used logistic regression analysis to estimate the chance of receiving RT in the western or the eastern region for breast or rectal cancer, adjusting for univariately significant determinants including age, gender (rectal cancer), stage (breast cancer), period of diagnosis, co-morbidity at diagnosis[12] and socio-economic status.[15]

Results

Total group

The annual number of newly diagnosed cancer patients increased by 73% from 5479 in 1988 to 9469 in 2006, the number of irradiated patients increased from 1668 to 2971, an absolute increase of 78%. During this period the annual percentage of patients receiving primary RT fluctuated between 30 and 32%, remaining at 30% in the western and becoming 35% in the eastern region in the period 2003-2006 (table 1). Patients older than 75 years were irradiated less often in both regions, although this also varied from about 18% in the western to 21% in 1988-1992 and 23% in 2003-2006 in the eastern region (table 1).

Tumour-specific application of primary RT is shown in table 2. The irradiated proportion of all newly diagnosed patients increased between 1988 and 2006 for patients with prostate or rectal cancer, but decreased for patients with lung or bladder cancer or with Hodgkin's lymphoma. After a decrease in the nineties an increase in the percentage irradiated patients with cervix or endometrial cancer was seen in more recent years. With most other tumour types it remained more or less unchanged, being slightly higher in the eastern region.

Table 1 - Percentage irradiated patients with cancer according to period of diagnosis, age and region in South Netherlands, 1988-2006

Period of diagnosis	Age of diagnosis (years)	Region	
		West	East
1988-1992	0-44	37.8	38.9
	45-59	38.1	38.3
	60-74	29.5	32.4
	≥75	19.9	20.9
	Total	30.1	31.6
1993-1997	0-44	36.1	34.9
	45-59	37.8	37.5
	60-74	28.9	31.9
	≥75	18.7	20.8
	Total	29.2	30.8
1998-2002	0-44	34.8	35
	45-59	33.4	38.3
	60-74	29.7	34
	≥75	17.4	22.4
	Total	28.1	32.3
2003-2006	0-44	36.6	39.3
	45-59	35.5	41.8
	60-74	32.3	37.3
	≥75	18.2	23.6
	Total	29.8	35

Breast cancer

The annual number of irradiated patients with breast cancer increased by more than 100% between 1988 (n=496) and 2006 (n=1005), while the total number of breast cancer patients simultaneously increased by 91%.

The percentages irradiated patients fluctuated annually between 57 and 62% for both the western and the eastern region until 1995 and then diverged to 69% in the eastern and 54% in the western region (figure 1). During the latter period a lower proportion of patients underwent breast-conserving surgery and a higher proportion mastectomy in the western than in the eastern region, while fewer mastectomy patients received RT in the western region. In 2006 the percentages of both surgical procedures seemed to converge to almost the same percentage in both regions, but this could not be seen yet in the percentages RT.

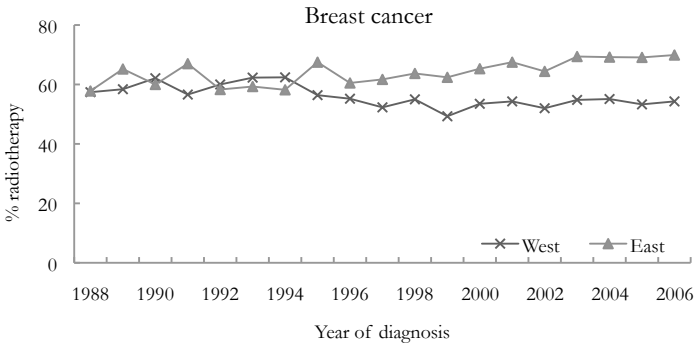

Figure 1: Radiotherapy for patients with breast cancer in South Netherlands, 1988-2006: according to catchment area (West and East)

Similar percentages of patients with stage I breast cancer were irradiated in the eastern and western regions in the late eighties and early nineties. In the western region the percentage decreased between 1994 and 1999 from 70 to 53%, followed by an increase to 65% in the last 4 years. In the eastern region a slight increase to 81% was seen over time (figure 2). The percentage irradiated patients with stage II disease in the eastern region fluctuated between 60 and 70% until 2000, and then stabilised at 60%. In the western region, however, a decrease was seen from 60 to less than 50% irradiated patients (figure 2). For patients with stage III disease no clear trend was found in either region, with again a higher percentage of patients being irradiated in the eastern than in the western region.

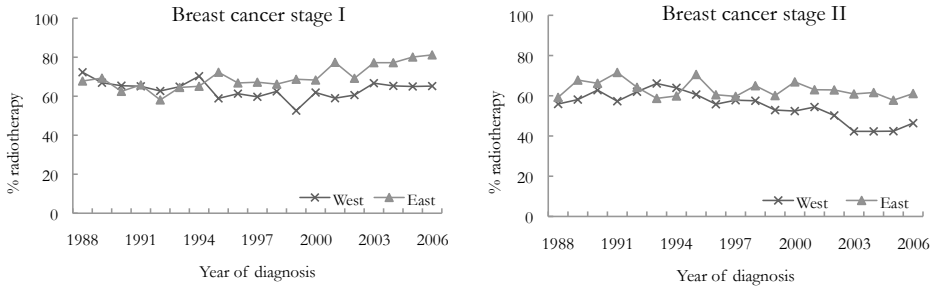

Figure 2: Radiotherapy for patients with breast cancer stage I and II in South Netherlands, 1988-2006: according to catchment area (West and East)

Differences between percentages irradiated patients in the two regions according to age are shown in figure 3. They are of course derived from the individual hospitals which refer patients for RT. The percentage irradiated patients from some hospitals was stable throughout time (no 1,2,3,5,10), for other hospitals it increased (6,9) or decreased (4,7,8) (figure 4).

The logistic regression analysis showed that patients with breast cancer from the eastern region were significantly more likely to receive RT than patients from the western region (OR=1.4, 95%CI=1.4-1.5).

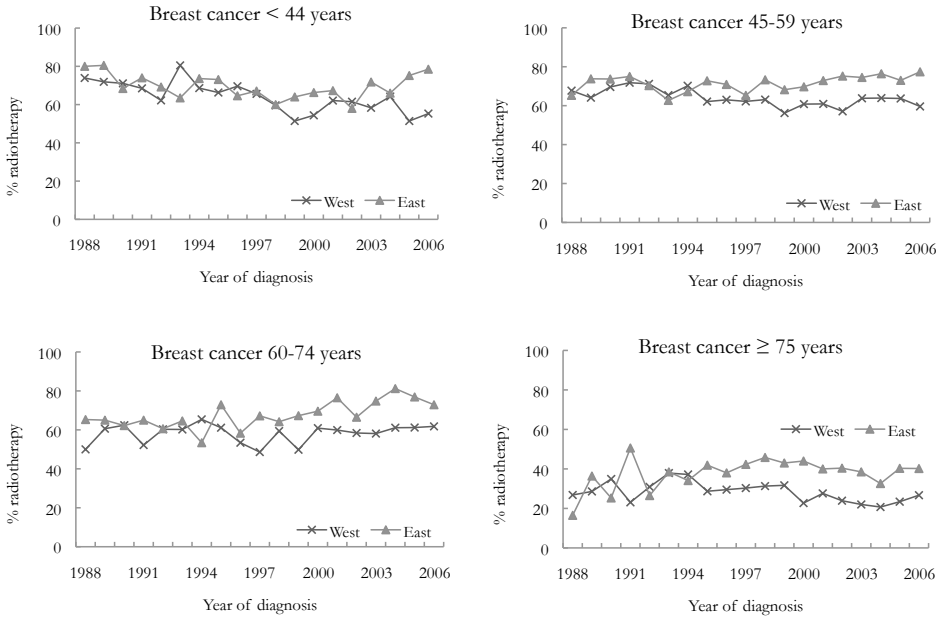

Figure 3: Radiotherapy for patients with breast cancer in South Netherlands, 1988-2006: according to catchment area (West and East) and age

Rectal cancer

The percentage patients with rectal cancer who received RT increased in 2003-2006 35% compared to the previous period, whereas the proportion receiving postoperative RT decreased from 1995 when preoperative RT was introduced. This implied short-course radiotherapy for resectable rectal cancer and long-course for locally advanced tumours, starting first in the eastern region: in 2004 50% of all patients with rectal cancer received preoperative RT and 25% underwent surgery without RT (figure 5). After 2004 a slight decrease was seen in the total percentage undergoing primary RT for rectal cancer (figure 6), due to a decrease in postoperative RT in the western region and a decrease in preoperative RT in both regions.

Patients with rectal cancer from the eastern region were significantly more likely to receive primary RT than patients from the western region (OR=1.4, 95%CI=1.3-1.6). This difference in RT (figure 6) was found for every age, the percentage irradiated patients older than 75 years being 10 to 15% lower than at middle age. The inter-hospital variation in RT use was large and did not converge in later years; nevertheless for every hospital an increase was seen over time (figure 4).

Table 2 - Trends in radiotherapy within 6 months of diagnosis in South Netherlands according to type of cancer, 1988-2006

	1988-1992			1993-1997			1998-2002			2003-2006		
	No. cancer patients	% RT	Share* RT (%)	No. cancer patients	% RT	Share RT (%)	No. cancer patients	% RT	Share RT (%)	No. cancer patients	% RT	Share RT (%)
Oral Cavity/Pharynx	154	40.3	0.7	225	44.4	0.9	236	42.4	0.8	183	54.6	0.8
Larynx	483	72.5	3.7	461	78.7	3.3	512	73.8	3	341	87.7	2.4
Esophagus	328	47.3	1.6	457	42	1.7	712	44.1	2.5	717	43.9	2.6
Lung	5479	43.8	25.2	5827	40.8	21.6	6228	33.8	16.6	5462	30	13.4
Breast	4945	60.3	31.4	6107	59.7	33.1	7342	58.5	33.8	6512	61.5	32.7
Cervix Uteri	418	51.9	2.3	420	43.1	1.6	368	45.4	1.3	299	49.2	1.2
Corpus Uteri	683	44.7	3.2	901	35.7	2.9	1005	26.9	2.1	936	31	2.4
Ovary	678	10.8	0.8	779	2.2	0.2	812	0.6	0	603	1.5	0.1
Rectum	1621	31.9	5.4	1868	37.4	6.4	2192	46.9	8.1	2086	63.3	10.8
Prostate	2278	20.1	4.8	3527	25	8	4423	32.6	11.4	5031	38.5	15.8
Testis	187	35.8	0.7	277	36.5	0	327	43.1	1.1	278	37.4	0.9
Urinary bladder	670	56.3	4	724	45.7	3	832	33.9	2.2	754	31.8	2
Hodgkin's disease	190	47.9	1	223	61.9	1.3	251	56.6	1.1	167	45.5	0.6
Non-Hodgkin lymphoma	944	22.4	2.2	1185	19.6	2.1	1352	23.4	2.5	1341	17.4	1.9
Myeloma	340	27.9	1	436	29.4	1.2	442	29.6	1	426	35.2	1.2
Central Nervous System	468	51.7	2.5	604	60.3	3.3	646	57.6	2.9	483	65.4	2.6
Soft Tissue	274	29.2	0.8	348	31	1	375	29.3	0.9	275	36.4	0.8
Primary Site Unknown	1507	2.5	0.4	1698	0.6	0	1914	2	0.3	1440	2	0.2
Other Sites†	9208	8.5	8.3	10610	7.7	7.4	12226	8.7	8.4	10527	8.7	7.5
Total#	30855	30	100	36677	30	100	42195	30.1	100	37861	32.3	100

*Share: the proportion of one irradiated tumour type relative to all tumours in that specific period of diagnosis

†All other invasive tumours except non-melanoma skin cancer

#Excluded: carcinoma in situ, superficial bladder cancer and non-melanoma skin cancer

Discussion

Total group

Although the total number of cancer patients and the number of irradiated patients both increased substantially during 1988-2006,[16] the percentage of patients who received RT within the framework of their primary treatment remained stable at about 30%. This stable percentage is made up of a rising percentage irradiated patients with prostate and rectal cancer and a decreasing percentage with lung and bladder cancer as well as Hodgkin's lymphoma. Despite the development of clear guidelines for the treatment of cancer patients which are easily accessible on the internet,[17] the percentage irradiated patients between the two regions we studied diverged over time. In the western region it increased gradually or remained stable for all ages, in the eastern region it increased for all ages. We found a lower referral rate for elderly patients in the western region; however there are no clear differences in geographical and socio-economical background.

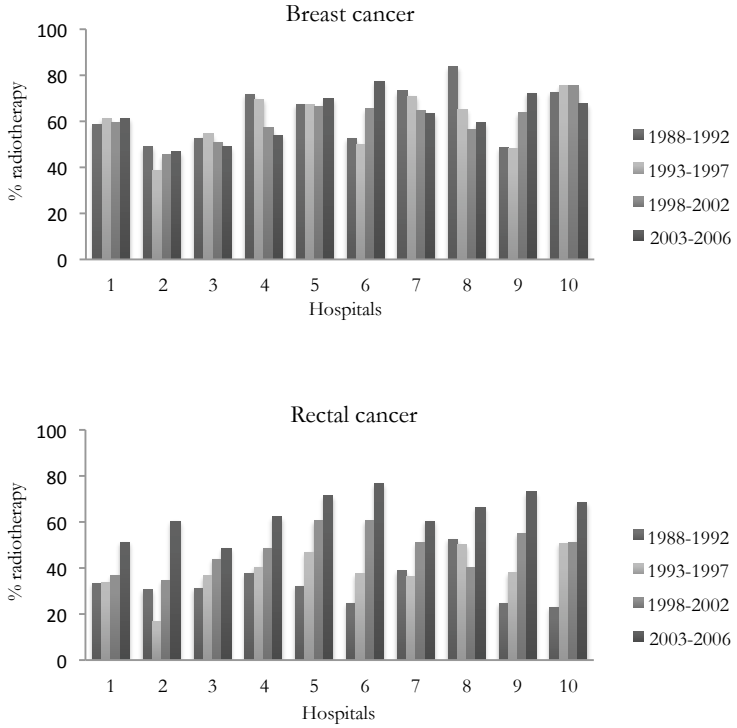

Figure 4: Radiotherapy for patients from community hospitals in South Netherlands, 1988-2006: 1,2,3,4 are hospitals in the western, 5,6,7,8,9,10 in the eastern region

We analysed patients with breast and rectal cancer in more detail, because breast cancer forms the largest group of patients in a RT department and national guidelines have been available for several years.[17] For rectal cancer too RT is an important part of the treatment, with significant changes in the nineties. For both of these tumour groups surgery is usually the primary treatment with RT postoperative or preceding surgery as for early stage rectal cancer. We found the largest differences between the eastern and the western region for patients with these tumours. A difference in referral policy between the eastern and western region might be the greater emphasis on clinical surgical research on rectal carcinoma and the intensive collaboration with the national trial organisation in the eastern region.[18]

In this study we defined primary RT as radiotherapy given within 6 months of diagnosis within the framework of the primary treatment. RT given within 6 months of diagnosis for metastases was not defined as primary RT. In earlier studies from our region covering parts of the same periods, this distinction was not made. Therefore, in the former, the percentages irradiated patients were 1-2 percent higher in both the western and the eastern region.[4, 5]

In our view the new guidelines for endometrial cancer, which were implemented in 2004 and which specified postoperative RT for stage I after a hysterectomy (RT for patients older than 60 years with stage Ia and Ib grade 3 or with stage Ic and for patients younger than 60 years with stage Ic grade 3)[17] might have increased the percentage irradiated patients with endometrial cancer in our last study-period in both regions, after a decrease caused mainly by the then ongoing PORTEC-trial evaluating the value of postoperative RT for patients with stage I endometrial cancer[5, 19, 20] and despite the negative side effects on quality of life among long term survivors.[21] For cervix cancer new guidelines promoted chemo-radiation for patients with stage IIb-IVa.[17, 22, 23]

The increasing percentage irradiated patients with prostate cancer through the years was the result of an increase in RT for elderly patients and also of an increase in patients both with localised and locally advanced tumours, while the portion of locally advanced tumours rose, especially in the last study-period. However for localised prostate cancer the treatment options, being radical surgery, external RT or brachytherapy, or watchful waiting,[17] are generally dependent on the patient's or doctor's preferences.[24, 25] We think that the encouraging results of several trials evaluating adjuvant hormonal treatment for patients with locally advanced tumours boosted referral for combined RT-hormonal treatment as well.[26-28] The preference of urologists in the eastern region for RT might explain the higher RT rates there.

Breast cancer

The introduction of mass screening for breast cancer between 1991 and 1996 led to a substantial increase in the absolute number of breast cancer patients. However, no increase was found in the percentage irradiated patients, probably because the percentage undergoing breast-conserving surgery (which gives, in combination with RT, the same results in terms of disease-free survival and survival as mastectomy[29-32]) in the age group eligible for screening (50-70 years, later up to 75) remained largely the same.[33]

We can explicate the divergence in referral rates for RT between the two regions since 1995 mainly from the differences in percentage breast-conserving surgery as follows: especially the percentage patients with stage I disease who underwent breast-conserving surgery increased during our whole study period in the eastern region, whereas it remained stable in the western region with a small increase in the last period. In both regions almost all of these patients received RT. For patients with stage II disease the percentage undergoing breast-conserving surgery has increased in both regions since 1995 (from 43 to 54 % in the eastern and 36 to 42% in the western region), but the percentage irradiated patients in this subgroup decreased (from 96 to 94% in the eastern and 96 to 89% in the western region). These decreases mainly explain the decrease in the total percentage RT for patients with stage II disease (figure 2).

Patients older than 75 years received RT less often, in the western region even less than in the eastern region. However, in elderly patients too, breast cancer does not behave as an indolent disease and RT after breast-conserving surgery should not be omitted.[34] Replacing RT by hormonal treatment is less safe and is subject to (other) side effects as well.[35, 36] Even after mastectomy RT might remain indicated for those with high-risk breast cancer.[37-39]

The differences in RT for breast cancer between the two regions reflected, in our opinion, the referral policy of the surgeons from the hospitals in the regions. For 5 hospitals the referral rates were more or less stable, with prominent low rates especially in the western region. A decreasing referral rate was seen in 3 and an increasing in 2 hospitals; this might be related to changes in the surgical staff. Variations in surgical treatment have also been found for other Dutch regions.[9, 40] Surgeons' characteristics, such as gender, degree or location of training, appear to be associated with breast conserving-surgery and the referral for RT.[10, 41, 42]

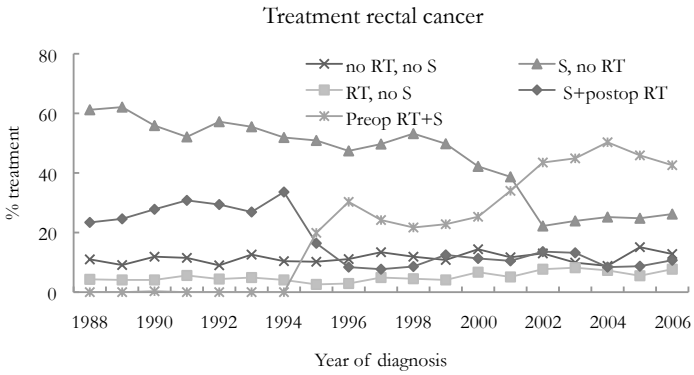

Figure 5: Time trend of primary treatment (%) of rectal cancer in South Netherlands, 1988-2006 (RT=radiotherapy, S=Surgery, postop=postoperative, preop=preoperative)

Rectal cancer

The large increase in percentage irradiated patients with rectal cancer in the period 2003-2006 can be clarified by the implementation of a short course of preoperative RT in both RT departments in the region as standard treatment for patients with clinically resectable rectal cancer.

Both departments participated in the Dutch TME-study between 1996 and 2000,[43] but the RT department in the eastern region had already introduced preoperative RT in 1994, while the department in the western region only started preoperative RT as standard treatment after publication of the results of the TME-study.[43] The surgeons and radiation oncologists in the eastern region have demonstrated a high scientific interest in rectal cancer.[44-47]

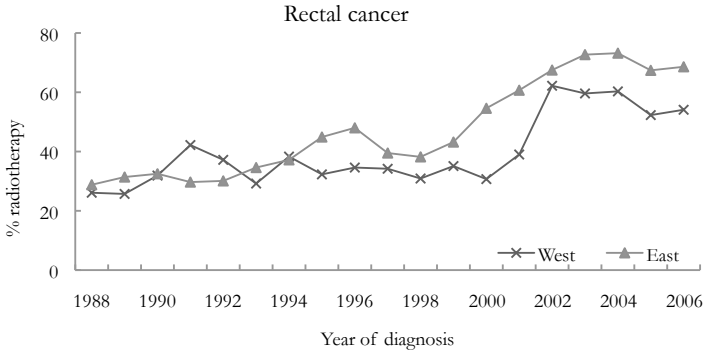

Figure 6: Radiotherapy for patients with rectal cancer in South Netherlands, 1988-2006: according to catchment area (West and East)

In our opinion the slight decrease in percentage RT after 2004 might be the result of publications regarding late side effects of short-course preoperative RT.[48, 49]

The percentage irradiated elderly patients in our region remained low after the implementation of preoperative RT. Less RT for elderly patients was described also in other recent population-based studies.[50] Although in the TME-study patients aged 75 years and older showed a better reduction of the local recurrence rate with preoperative RT compared to younger patients, distant metastasis free survival, cancer free survival and 5-years survival did not improve. Postoperative complications were a major problem in the elderly, especially in the first 6 months after surgery, compared with younger patients.[18, 46] Delayed surgery after a short course of preoperative RT might be an option, especially for elderly patients to decrease the combined risks of surgery and RT while still depending on their important role in the prevention of local recurrences.

We did not include stage of rectal cancer in this study, because preoperative stage was often unknown, and postoperative stage might have become lower, especially after a long course of preoperative irradiation.[51, 52]

Conclusion

Although the absolute number of irradiated patients with cancer increased substantially during 1988-2006, the proportion of referred patients remained stable in the south of the Netherlands.

Between the eastern and the western parts of the region, each with their own RT departments and referring hospitals, substantial variations were found in referral rates for RT, especially in later years. The question is whether this divergence might have been larger if there had not been guidelines and multidisciplinary oncology meetings.

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Chapter 3

Cohort studies

3.1

A population-based study of radiotherapy in a cohort of patients with breast cancer diagnosed between 1996 and 2000

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Abstract

We studied the use of radiotherapy (RT) (especially secondary RT) in a cohort of 6561 patients in South Netherlands with invasive breast cancer diagnosed between 1996-2000 (median follow up: 66 months, range 0-107 months). Radiation within 6 months of diagnosis was considered primary RT (PRT). RT given 6 months or later after diagnosis or after PRT was considered secondary RT (SRT). Of all patients, 67% received RT, 3554 only PRT, 323 only SRT and 503 both. The cumulative use of SRT at 100 months was 17%. The 826 patients receiving SRT underwent 1846 courses 0-105 months (median 36) after diagnosis; the retreat-rate was 35%. Elderly patients received SRT significantly less often ($OR_{age\ 50\text{-}69}$=0.7, 95%CI=0.6-0.8, $OR_{age\ \geq 70}$=0.4, 95%CI=0.3-0.5). The following factors increased the chance for SRT: patients from the eastern region (OR=1.3, 95%CI=1.1-1.6); patients who received PRT (OR=1.3, 95%CI=1.0-1.5) and patients who underwent mastectomy including axillary node dissection as well as unresected patients (OR=1.9, 95%CI=1.5-2.4, OR=2.6, 95%CI=1.7-3.9, respectively).

Thirteen percent of all patients with breast cancer received SRT, with a large variation in age and between the 2 RT departments in the region.

Introduction

The incidence of breast cancer in the south of the Netherlands amounted to 120 per 100,000 women in 2000. Radiotherapy (RT) is an essential part of breast cancer treatment, either as part of the primary treatment within the framework of breast-conserving treatment or mastectomy,[1-3] or for palliation of recurrent or metastatic breast cancer. [4, 5] Therefore patients with breast cancer constitute a large proportion of the patients treated in a RT department.

Of all cancer patients about 50% are likely to receive radiotherapy during the course of their disease.[6, 7] This percentage is not derived from population-based studies but is nevertheless often used in the process of decision-making for estimation of the future capacity of RT equipment and personnel needed. The overall percentage usually consists of a mixture of primary RT (PRT) as part of the initial treatment and secondary RT (SRT) in the case of recurrent disease or metastases without taking into account whether patients had already received primary RT.[6, 8] In a population-based study of patients treated with RT as part of their primary treatment we found that 30% of all cancer patients received PRT.[9, 10] For patients diagnosed with breast cancer in 1998-2002 this amounted to 55%.[9] SRT has been studied in our region for all cancer patients diagnosed between 1975 and 1989: 5% of previously non-irradiated patients received RT for recurrent disease or metastases, and about 40% of all irradiated patients had RT again.[11] Recent studies used an evidence-based approach to determine the use of RT as part of primary treatment and for treatment of recurrences or metastases. They estimated that 66% to 83% of all breast cancer patients received RT during the course of their illness.[12, 13]

Since we had already performed several studies on the use of primary RT we wanted to estimate the percentage of patients receiving RT during their illness, which can also be relevant for planning purposes. We determined, in a population-based setting in a region with 2 large RT departments, the proportion of patients with breast cancer who received RT as part of their primary treatment and as SRT. We explored the influence of patient and tumour characteristics on SRT and variations in referral for SRT.

Methods

We studied a cohort of patients with a first invasive breast cancer, diagnosed between 1st January 1996 and 31st December 2000 and followed until 1st January 2005. Data were derived from the population-based Eindhoven Cancer Registry (ECR), which has recorded data on all patients newly diagnosed with cancer since 1955. The registry covers a large part of South Netherlands with approximately 2.4 million inhabitants in 2004. The medical infrastructure consists of six Pathology departments, hospital medical records offices in 10 general hospitals and two large RT departments (one in the western (Tilburg) and one in the eastern (Eindhoven) part of the region). Patients never have to travel more than one hour to a RT department.

Table 1 - Characteristics of patients with breast cancer diagnosed between 1996 and 2000 (n=6561) receiving primary radiotherapy in South Netherlands

Patient characteristics	Primary radiotherapy		
	No (n=2504) (%)	Yes (n=4057) (%)	Total (n=6561) (%)
Age at diagnosis			
≤ 49 years	554 (22)	1142 (28)	1696 (26)
50 t/m 69	1002 (40)	2059 (51)	3061 (47)
≥70 years	948 (38)	856 (21)	1804 (28)
Number of concomitant diseases			
None	1188 (47)	2441 (60)	3629 (55)
One	580 (23)	889 (22)	1469 (22)
2+	387 (16)	372 (9)	759 (12)
Unknown	349 (14)	355 (9)	704 (11)
Socio-economic status			
Low	687 (28)	977 (24)	1664 (25)
Middle	927 (37)	1669 (41)	2596 (40)
High	660 (26)	1249 (31)	1909 (29)
Institution[a]	195 (8)	131 (3)	326 (5)
Unknown	35 (1)	31 (1)	66 (1)
Stage at diagnosis			
I	897 (36)	1713 (42)	2610 (40)
II	1135 (45)	1815 (45)	2950 (45)
III	133 (5)	390 (10)	523 (8)
IV	176 (7)	105 (3)	281 (4)
Unknown	163 (7)	34 (1)	197 (3)
Second breast tumour			
No	2377 (95)	3847 (95)	6224 (95)
Yes	127 (5)	210 (5)	337 (5)
Vital status 1-1-2005			
Alive	1664(66)	3068 (76)	4732 (72)
Deceased	840 (34)	989(24)	1829 (28)
Surgery[b] (western region)			
BCS + AC	432 (3)	1227 (67)	1269 (39)
BCS	62 (4)	32 (2)	94 (3)
MRM + AC	1074 (76)	510 (28)	1584 (49)
MRM	63 (4)	25 (1)	88 (3)
No surgery	176 (12)	41 (2)	217 (7)
Surgery (eastern region)			
BCS + AC	53 (5)	1632 (73)	1685 (51)
BCS	51 (5)	35 (2)	86 (3)
MRM + AC	840 (77)	502 (23)	1342(41)
MRM	28 (3)	18 (1)	46 (1)
No surgery	115 (11)	35 (2)	150 (5)
Radiotherapy Department			
Western region	1417 (57)	1835 (45)	3252 (50)
Eastern region	1087(43)	2222 (55)	3309 (50)
Secondary Radiotherapy			
No	2181 (87)	3554 (88)	5735 (87)
Yes	323 (13)	503 (12)	826 (13)

[a] institution: patients living in an institution (i.e. nursing home)
[b] BCS=Breast-conserving surgery, AC=axillary clearance, MRM=modified radical mastectomy

Trained registry personnel from the ECR actively collects data on diagnosis, staging, co-morbidity and primary treatment, given or planned within 6 months of diagnosis, from the hospital charts after notification of newly diagnosed cases by the regional Departments of Pathology, Haematology and Radiotherapy as well as the national Registry of Hospital Discharge Diagnoses. An indicator of socio-economic status (SES) was developed by Statistics Netherlands based on individual fiscal data (economic value of the home and household income) and provided at aggregated levels for each postal code (average of 17 households). Socio-economic status was categorised 1 (low) to 3 (high), with a separate class for postal codes with a care-providing institution (such as a nursing home).

Cancer registries in the Netherlands usually cover over 95% of all cases, due to the infrastructure of and good access to Dutch health care facilities, together with the multiple source notification procedures used.[14] In both RT Departments each course of RT is recorded with date of onset, patient characteristics and treatment protocol number indicating the kind of radiation treatment given. Data on all patients with breast cancer who received RT between 1st January 1996 and 1st January 2005 at the two RT Departments were combined with the above-mentioned data from the ECR.

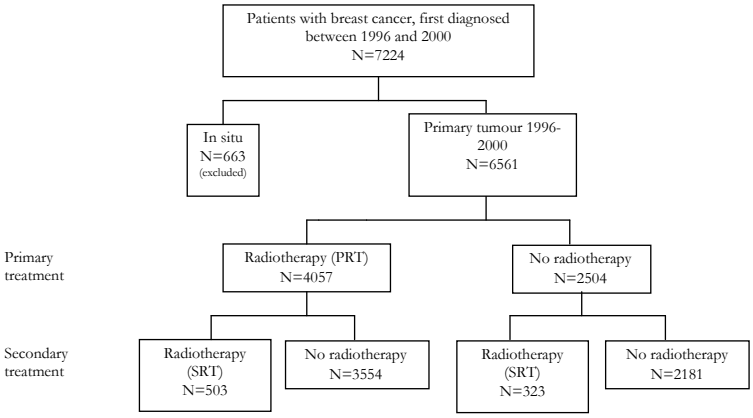


Figure 1: Flow chart of the study-population: breast cancer patients diagnosed between 1996 and 2000 in South Netherlands (PTR=primary radiotherapy, SRT=secondary radiotherapy)

Between 1996 and 2000, a total of 7224 patients were first diagnosed with breast cancer, including sarcomas (n=55) and unknown morphology (n=38). Patients with carcinoma in situ (n=663) were excluded. We only considered RT given for the first tumour. Eventually we included 6561 patients with invasive breast cancer in our analysis (figure 1).

Radiation given or planned within 6 months of diagnosis was considered PRT.[15]

This includes patients irradiated within 6 months of diagnosis only for metastases as planned primary treatment (n=64). We also included patients who were irradiated as part of primary treatment later than 6 months after diagnosis (in case of prolonged chemotherapy) (n=86).

Table 2 - Odds of receiving secondary radiotherapy for patients with breast cancer diagnosed between 1996 and 2000 (n=6561) in South Netherlands, each variable adjusted for all others

	Odds-ratio	95%CI	p-value
Age at diagnosis			
≤49 years	1		
50 t/m 69	0.7	0.6-0.8	<0.0001
≥70 years	0.4	0.3-0.5	<0.0001
Number of concomitant diseases			
None	1		
One	0.9	0.8-1.1	0.5
2+	0.8	0.6-1.1	0.1
Unknown	1	0.7-1.2	0.7
Socio-economic status			
Low	1		
Middle	1	0.9-1.3	0.7
High	1.1	0.9-1.4	0.4
Institution[a]	0.8	0.5-1.3	0.4
Unknown	1.4	0.7-2.9	0.4
Stage at diagnosis			
I	1		
II	2.2	1.8-2.7	<0.0001
III	2.9	2.1-3.9	<0.0001
IV	8	5.5-11.5	<0.0001
Unknown	0.9	0.5-1.7	0.8
Radiotherapy department			
Western region	1		
Eastern region	1.3	1.1-1.6	0.0003
Primary radiotherapy			
No	1		
Yes	1.3	1.0-1.5	0.02
Second breast tumour			
No	1		
Yes	1	0.7-1.5	0.8
Surgery[b]			
BCS + AC	1		
BCS	1.6	0.9-2.8	0.09
MRM + AC	1.9	1.5-2.4	<0.0001
MRM	1.7	1.0-3.0	0.07
No surgery	2.6	1.7-3.9	<0.0001

[a] institution: patients living in an institution (i.e. nursing home)
[b] BCS=Breast-conserving surgery, AC=axillary clearance, MRM=modified radical mastectomy

RT given 6 months or later after diagnosis (other than the above) or RT given after a previous course of radiation for breast cancer (even within 6 months) was considered as delayed or SRT. Patients first irradiated for metastases within 6 months of diagnosis, but for whom this irradiation was not planned as primary treatment, were also considered to have received SRT (n=57).

When data from the RT institutes were compared with data from the ECR we found that PRT was not registered in the ECR in 136 cases (2% of the total cohort). We included them in our analysis as part of the PRT group. RT registered in the ECR for 2 patients who were treated later than 6 months (25 and 51 months) after diagnosis was considered to be SRT. Twenty-one patients were treated with a combination of hyperthermia and external RT for recurrent breast cancer, all administered in the RT department at the Western region, which is a top level reference department for superficial hyperthermia.[16] Eleven of these patients received previous PRT at the same department, and 9 in the other; 1 had previous SRT for recurrent breast cancer in the same institute.

The retreat-rate is defined as the number of radiation courses given after the first course divided by the number of all first courses either as PRT or as SRT (=number of patients irradiated).

Table 3 - Number of secondary radiation courses (range:0*-105 months after primary diagnosis) per patient in a cohort of breast cancer patients diagnosed between 1996-2000 (n=6561) in South Netherlands

Number of secondary radiotherapy courses	Number of patients (%)	Total number of secondary radiotherapy courses	Cumulative number of secondary radiotherapy courses
1	438 (53)	438	438
2	166 (20)	332	770
3	76 (9.2)	228	998
4	47 (5.7)	188	1186
5	44 (5.3)	220	1406
6	14 (1.7)	84	1490
7	13 (1.6)	91	1581
8	11 (1.3)	88	1669
9	5 (0.6)	45	1714
10	4 (0.5)	40	1754
11	6 (0.7)	66	1820
12	0 (0)	0	1820
13	2 (0.2)	26	1846
Total	826 (100)	1846	1846

*0 months after diagnosis: patients first irradiated for metastases within 6 months of diagnosis, but for whom this irradiation was not planned as primary treatment

Characteristics of patients who did or did not receive PRT are listed in table 1. For surgery we distinguished between patients from the western and the eastern region.

We used logistic regression analysis to estimate the chance of receiving SRT adjusting for age, number of concomitant conditions, socio-economic status, stage, second breast tumour, RT institute, primary surgical treatment and prior PRT. We assessed the number of patients receiving SRT, and the number and type of secondary radiation treatments (for recurrent or for metastasised disease) they received.

The cumulative use of any RT (PRT or SRT) over time was calculated according to the Life Table Method,[17] starting on the date of diagnosis and ending on the date of start of RT, or censored on the date of death or 1st January 2005 whichever occurred first. In total 1543 patients were censored on 1st January 2005. The cumulative use of SRT was calculated by means of the same method: follow-up for patients who received PRT (n=4057) started on the last day of primary RT (according to the definition, these patients were at risk for SRT after having received PRT); follow-up for patients who received no PRT (n=2385, 119 patients died within 6 months of diagnosis) started 6 months after diagnosis (by definition patients without PRT were at risk for SRT 6 months after diagnosis). Follow-up of both groups ended on the date of initiating SRT, date of death or 1st January 2005, whichever occurred first. These 2 groups were compared by means of the log-rank test.

Results

In our cohort of 6561 patients with breast cancer diagnosed between 1996 and 2000, (median follow-up 66 months, range 0-107 months), 4380 (67%) patients received RT between 1st January 1996 and 1st January 2005: 3554 (54%) only PRT, 323 (5%) only SRT and 503 (8%) both (figure 1). Five hundred and three patients who received PRT and 120 patients who received only SRT were irradiated twice or more. The retreat rate was 35% (1523/4380). The patient characteristics are listed in table 1. About half of all patients underwent breast-conserving surgery and half mastectomy. In the eastern region a higher percentage received breast-conserving surgery and was referred for PRT. Five percent of the patients (n=337) developed a second breast tumour between 1st January 1996 and 1st January 2005, 146 (43%) of whom received PRT for the second tumour. Six patients developed a second tumour in the ipsilateral breast, but with other morphology or at another sub localisation, 331 in the contralateral breast. For 105 patients the second tumour was diagnosed within 1 month of the first, for 82 of these patients on the same day. In this study we only considered RT given for the first tumour (n=57). The odds for receiving SRT are shown in table 2. Patients aged 50 years or older received SRT significantly less often (OR=0.7, 95%CI=0.6-0.8 and OR=0.4, 95%CI=0.3-0.5 for patients 50-69 years and 70 years or older, respectively). Patients with an initial tumour stage higher than stage I received SRT significantly more often (stage II: OR=2.2, 95%CI=1.8-2.7, stage III: OR=2.9, 95%CI=2.1-3.9, stage IV: OR=8, 95%CI=5.5-11.6). Patients from the eastern region were referred more often for SRT (OR=1.3, 95%CI=1.1-1.6). Patients who received PRT had a slightly higher chance of receiving SRT (OR=1.3, 95%CI=1.0-1.5).

Patients who underwent mastectomy including axillary node dissection and patients who did not undergo surgery had SRT significantly more often (OR=1.9, 95%CI=1.5-2.4, OR=2.6, 95%CI=1.7-3.9, respectively).

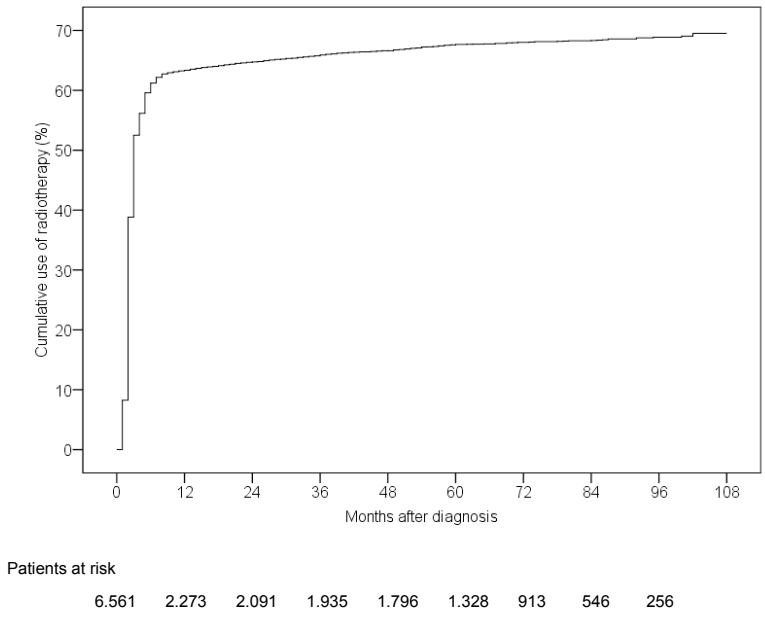
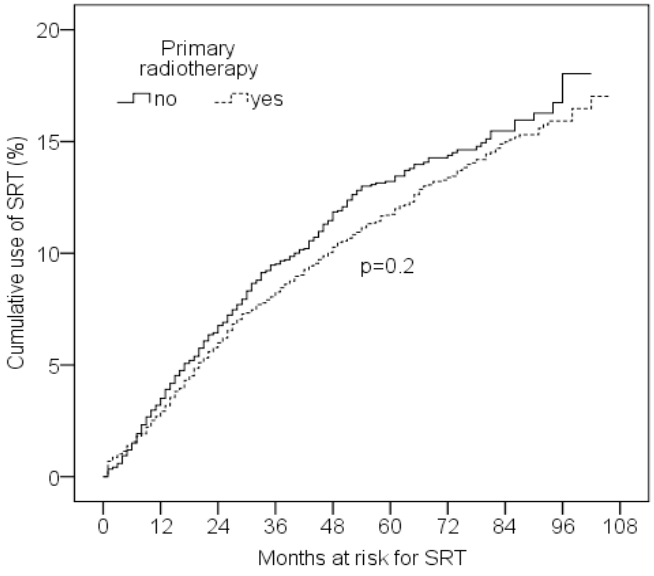


Figure 2: Cumulative use of radiotherapy (primary or secondary) in a cohort of breast cancer patients (n=6561) diagnosed between 1996 and 2000 in South Netherlands

Of 826 patients receiving SRT, 138 (17%) had the first course of SRT for a recurrence and 688 for metastases; they underwent 1846 courses in total, with a range of 0-101 months (median 36 months) after primary diagnosis: 174 courses for relapsed breast tumours and 1672 courses for metastases. Seventy-four percent of these patients had more than one secondary treatment (median=3) (table 3).

Figure 2 shows the cumulative use of RT, either PRT or SRT. Of all patients at risk, 4035 (61%) had RT within the first 6 months of diagnosis. After 101 months 4380 patients had received RT, or 67% of the patients at risk. In figure 3 the cumulative use of SRT is shown separately for patients who did or did not receive previous PRT.

The total cumulative use of SRT was 17% 100 months after start of follow-up. The cumulative chance to have SRT was slightly higher for patients who did not receive prior PRT (p=0.2).



Patients at risk

No	PRT:	2.385	2.182	2.007	1.858	1.571	1.123	381	381	115
	PRT:	4.057	3.819	3.598	3.409	2.977	2.160	1.449	859	350

Figure 3: Cumulative use of secondary radiotherapy for patients who did or did not receive primary radiotherapy in a cohort of breast cancer patients (n=6561) diagnosed between 1996 and 2000 in South Netherlands (PTR=primary radiotherapy, SRT=secondary radiotherapy)

Discussion

We studied the percentage of patients with breast cancer in a cohort diagnosed between 1st January 1996 and 31st December 2000 in our region who received either primary or secondary RT. With a median follow-up of 66 months, 67% of all breast cancer patients received RT at some point in the course of their illness. This is similar to an evidence-based estimation for optimal RT utilisation in Canada, while an evidence-based study in Australia calculated a higher level.[12, 13] However, reported actual RT utilisation rates were much lower (25-50%),[18, 19] except in the state of New South Wales, Australia (71%) which was the only study that included patients who had their first RT late during the course of their disease.[20]

We found that patients older than 50 years of age had a significantly lower chance of receiving SRT than younger patients. Manders and colleagues described the clinical management of women with metastatic breast cancer, demonstrating that patients aged 70 years or older were less likely to receive both chemotherapy or RT.[21] Elderly patients were also treated less often with primary irradiation, sometimes related to co-morbidity.[22, 23]

Socio-economic status did not affect the chance to receive SRT in our cohort (table 2), while in the USA large treatment disparities were found.[24]

However, socio-economic disparities in the Netherlands are relatively small and medical insurance covers cancer treatment for 99% of the population.[25]

The chance to receive RT for an invasive carcinoma may have been influenced by a previous carcinoma in situ (CIS). According to the national guidelines duct carcinoma in situ (DCIS) should be treated with breast-conserving surgery, including RT, or alternatively with a simple mastectomy on indication.[26] Currently 49% of patients with DCIS are irradiated but in 1996 this was only 20%.[27] After breast-conserving therapy, including irradiation for a previous DCIS, no standard RT is possible for a new invasive tumour in the same breast. As a result patients with an invasive carcinoma after earlier treatment for DCIS are more likely to undergo a mastectomy without irradiation. DCIS forms 8% (in 1996) to 10% (in 2003) of all new breast tumours.[28]

In our cohort 337 (5%) patients developed a second breast tumour between 1st January 1996 and 1st January 2005. This percentage was also found in another population-based study.[29] Because we only considered RT given for the first tumour, we excluded these second tumours, 43% of which received PRT, from our cohort. If these patients received SRT, we distinguished for which tumour on the basis of data from the RT departments. Only SRT for the first tumour was included in our study. A second breast tumour did not influence the chance of receiving SRT for the first tumour.

When a local recurrence occurs after mastectomy (66% of patients primarily undergoing a mastectomy received no PRT), the recurrent tumour can often be treated with SRT. Patients with a recurrence after breast conserving-treatment (97% of whom received PRT) are usually not suited for RT for their recurrence. Therefore a mastectomy will commonly be the first treatment of choice. Some of these patients are eligible for regional lymph node irradiation. Superficially located recurrent breast cancer in a previously irradiated area can be treated with RT in an adapted fractionation schedule combined with hyperthermia as radiosensitizer.[16]

In the eastern region a higher percentage of patients were treated with breast-conserving surgery, which leads to a higher percentage of patients receiving PRT in that region. This can be explained by variations in surgical management, which are larger in the western region than in the eastern region.[30, 31] This variation in referral for radiotherapy was observed not only for PRT but also for SRT.

Patients with a higher stage, usually treated with mastectomy including axillary node dissection, have a higher risk for metastases amenable to RT. Patients who did not have any surgery at all had a significantly higher chance of receiving SRT, probably because almost 50% of them had a stage IV tumour at diagnosis, thus a higher risk for symptomatic metastases amenable to RT. Eventually, skeletal metastases occur in 20-40% of patients with breast cancer.[32, 33] RT relieves pain in most cases, is effective in spinal cord compression and can prevent a pathological fracture in the case of lytic lesions of the bone cortex.[34-36] It also improves quality of life and may prolong median survival for most patients with symptomatic brain metastases which occur in 10-20% of women with metastatic breast cancer.[37]

The cumulative use for SRT was slightly higher for patients who did not receive prior PRT (figure 3), but after adjustment, the chance of receiving SRT was 30% higher for patients with prior PRT in comparison with patients without prior PRT (OR=1.3, table 2). This can partly be explained by the differences in stage distribution and variations in surgical procedures.

A potential drawback of our study is the median follow-up time for our cohort (66 months, range 0-107), which is not very long for a population of breast cancer patients. However, we were unable to study an earlier cohort, because data were incomplete before 1996. Although the development of loco-regional recurrences after 5 years is not uncommon,[38] the majority of recurrences and distant relapses occur in the first 5 years.[39-41] Generally, breast cancer often behaves as a chronic disease for many patients, resulting in prolonged survival with metastases.[41, 42] Patients with metastasised disease may be referred for the first SRT many years after the first appearance of the disease and can be treated with irradiation on different locations until their death. Only 28% of patients in our cohort had died on 1st January 2005. So, whereas the majority of SRT for recurrent breast cancer will occur within our study period, illustrated by the levelling off of the total referral rate (PRT and SRT) after the first year of follow-up (figure 2), the cumulative use of SRT (17% at 100 months after the start of follow-up) will undoubtedly continue to increase slowly over subsequent years.

Conclusions

The required capacity for RT for breast cancer is likely to be higher than the cumulative rates calculated now, requirements also need to be based on RT for DCIS (now 10% of all breast cancers, 50% of whom receive RT), and the RT for second primary breast cancer. Furthermore, there was a relatively low rate of breast-conserving surgery (and thus PRT) attributable to several referring specialists[30, 31] and there was also some under-treatment of elderly patients.[22, 23] This approach to the investigation of radiotherapy consumption stimulates discussion on optimal treatment and clinical justification of treatment variations. Therefore continued monitoring and discussion with referring specialists is highly warranted.

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3.2

A population-based study of radiotherapy in a cohort of patients with rectal cancer diagnosed between 1996 and 2000

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Abstract

Aims

To study, in a population-based setting, the use of delayed radiotherapy (RT) in a cohort of 2008 unselected rectal cancer patients diagnosed between 1996-2000.

Patients and Methods

Radiation within 6 months of diagnosis was considered part of the primary treatment (PRT). RT given 6 months or later after diagnosis or after PRT was considered as delayed or secondary RT (SRT). Number, percentage and cumulative proportion of patients receiving SRT were calculated. The odds for receiving SRT (total and for recurrent rectal cancer only) were studied by logistic regression analysis, taking into account age, gender, co-morbidity, socio-economic status, stage, prior PRT and RT department (2 departments, each serving general hospitals only).

Results

Forty-six percent of all newly diagnosed patients received RT. Ten percent (n=203) received at least once SRT, either after PRT or as first RT, of which 96 patients for a relapsed rectal tumour (31 after PRT on the rectal tumour, 65 as a first radiation treatment). In a multivariate analysis of patients with rectal recurrence secondary pelvic irradiation was less often given after primary irradiation (OR=0.7, 95%CI=0.4-1.1). Patients with a stage III significantly more often received SRT on a recurrence (OR=2.5, 95%CI=1.4-4.5). Generally, patients in the eastern department received more often PRT and less often SRT for recurrence (OR=0.5, 95%CI=0.3-0.8).

Conclusions

Five percent of all patients with rectal cancer received SRT on a recurrent tumour, with a large variation between the two RT departments in the region.

Introduction

The incidence of rectal cancer in the Netherlands was 26 per 100,000 for men and 13 per 100,000 for women in 2002. Radiotherapy (RT), pre- and postoperative or for palliation, plays an important role, especially since the results of the Total Mesorectal Excision study were published.[1, 2] Of all newly diagnosed cancer patients about 50% are generally assumed to receive radiotherapy during the course of their disease.[3, 4] Although not derived from population-based studies this percentage is nevertheless often used in the process of decision-making on required capacity of RT equipment and personnel. The overall percentage usually consists of a mixture of immediate or primary RT (PRT) as part of the initial treatment and delayed or secondary RT (SRT) in the case of recurrent disease or metastasis[3, 5] without taking into account whether patients had already received primary RT. In a population-based study of patients treated with RT as part of their primary treatment about 30% of all cancer patients had received PRT,[6, 7] being 43% for patients diagnosed with rectal cancer in 1998-2002.[6] In our region SRT had already been studied for the total group of cancer patients, of whom 40% received RT for the first time as part of the primary treatment or for recurrent disease or metastases in 1986 and 1987.[8]

Recent studies used an evidence-based approach to determine the use of RT as part of primary treatment and as part of the treatment of recurrence or metastases. Of all rectal cancer patients 61-72% were estimated to receive RT during the course of their illness.[9, 10] Having performed several studies on the use of primary RT we wanted to estimate the percentage of patients receiving RT during their illness, which can also be relevant to planning purposes.

We studied a region of 2.4 million people with 2 large RT departments and determined the proportion of patients with rectal cancer receiving RT as part of their primary treatment and as secondary RT. We also explored the influence of covariates on SRT.

Patients and Methods

Study population

We studied, in a population-based setting, a cohort of patients with rectal cancer, diagnosed between 1st January 1996 and 31st December 2000 and followed until 1st January 2005. Data were derived from the population-based Eindhoven Cancer Registry (ECR), which has recorded data on all patients newly diagnosed with cancer since 1955. The registry covers a large part of South Netherlands with approximately 2.4 million inhabitants in 2004. It is supported by six Pathology Departments, hospital medical records offices in 10 general hospitals and two large RT departments (one in the western (Tilburg) and one in the eastern (Eindhoven) part of the region so that patients never have to travel for more than one hour).

Trained registry personnel actively collects data on diagnosis, staging, co-morbidity and primary treatment, given or planned within 6 months of diagnosis, from the hospital charts after notification of newly diagnosed cases by the regional departments of Pathology, Haematology and Radiotherapy as well as the national Registry of Hospital Discharge Diagnoses. Socio-economic status (SES) was defined as either low, medium or high based on fiscal data on income and the value of the house determined for each postal code in residential areas (average: 17 households). Cancer registries in the Netherlands usually cover over 95% of all cases, thanks to the infrastructure of and good access to Dutch health care facilities, together with the multiple source notification procedures used.[11]

Between 1996 and 2000, a total of 2043 patients were diagnosed with invasive rectal cancer. Patients with unknown morphology (n=28), malignant melanoma of the rectum (n=3), leiomyosarcoma (n=2), or a cytological diagnosis only (n=1) were excluded. We also excluded a patient diagnosed with rectal cancer at autopsy, leaving 2008 patients for analysis.

Radiotherapy

In both RT departments, each serving only community hospitals, each course of radiation (primary or secondary) is recorded with date of onset, patient characteristics and treatment protocol number indicating the kind of radiation treatment given. Data on all patients with rectal cancer who received RT between 1st January 1996 and 1st January 2005 at the two RT departments were combined with the above-mentioned data from the ECR.

Radiation given within 6 months of diagnosis was considered as PRT. RT given 6 months or later after diagnosis or RT given after a previous course of radiation for rectal cancer was considered as delayed or SRT (RT for a recurrent rectal tumour or for metastases). When data from the RT institutes were compared with data from the ECR we found that PRT was not registered in the ECR in 14 cases. We considered them as part of the PRT group. PRT was registered in the ECR for 4 patients who were treated later than 6 months after diagnosis; they were considered as part of the SRT group.

The RT department in the eastern part of the region is a highest level reference department, especially for recurrent tumours. Here intraoperative electron beam radiation therapy (IORT) could be given as a supplement to external preoperative RT for fixated or locally recurrent rectal cancer.[12] The medical records of patients who were registered with the treatment protocol for IORT (n=83) were checked. Nineteen of these cases received only external RT; IORT was not given because metastases were detected during surgery, the rectal tumour appeared to be inoperable, or an area of risk could not be indicated because the tumour had been removed completely. In all other cases we considered the combined therapy, including IORT, as one treatment (n=43 for primary and n=21 (one patients 2 times) for secondary treatment), also when external beam RT was given in the other RT Department (n=15).

The retreat-rate is defined as the number of radiation courses given after the first course divided by the number of all first courses.

Table 1 - Patient characteristics and multivariate analysis of patients with rectal cancer diagnosed between 1996 and 2000 receiving secondary radiotherapy (RT) in South Netherlands

Patient characteristics	Secondary RT		Multivariate[a]
	No (n=1805)	Yes (n=203)	OR[b] (95%CI[c])
Gender			
Male	1061	124	1
Female	744	79	0.9 (0.7-1.3)
Age at diagnosis			
70 years or younger	979	137	1
70+ years	826	66	0.7 (0.5-0.9)
Number of concomitant diseases			
None	767	106	1
One	516	50	0.8 (0.6-1.2)
2+	363	33	0.8 (0.5-1.2)
Unknown	159	14	0.7 (0.4-1.4)
Socio-economic status			
Low	492	57	1
Middle	672	82	1.0 (0.7-1.4)
High	516	58	0.9 (0.6-1.3)
Institution[d]	105	5	0.5 (0.2-1.1)
Unknown	20	1	0.4 (0.1-3.2)
Stage			
I	512	28	1
II	446	44	1.8 (1.1-3.0)
III	361	74	3.7 (2.3-5.8)
IV	292	40	2.5 (1.5-4.1)
Unknown	194	17	1.8 (0.9-3.3)
PRT[e]			
Western region: no	554	56	1
Western region: yes	274	36	1.0 (0.7-1.6)
Eastern region: no	533	53	1.0 (0.6-1.6)
Eastern region: yes	444	58	0.9 (0.6-1.4)
Vital status 1-1-2005			
Deceased	937	178	
Alive	868	25	

[a]Multivariate analysis: each variable is adjusted for all others, except for vital status
[b]OR=Odds Ratio
[c]95%CI=95% Confidence Interval
[d]Institution: patients living in an institution (i.e. nursing home)
[e]PRT=primary radiotherapy

Statistical analysis

Differences in the distribution of determinants of SRT between patients who did or did not receive SRT were tested with the chi-square test. We used logistic regression analysis to estimate the chance of receiving SRT (for recurrence and metastases, and for recurrence alone) adjusting for age, gender, number of concomitant conditions, socio-economic status, stage, prior PRT and RT department.

We assessed the number of patients receiving SRT, and the number and type of secondary treatments (for recurrent or for metastasised disease) these patients received.

The cumulative risk of receiving any RT (PRT or SRT) over time was calculated according to the Life Table Method,[13] starting on the date of diagnosis and ending on the date of start of RT, date of death or 1st January 2005 (median time of follow up 49 months, range 0-107 months), whichever occurred first. The cumulative risk of receiving SRT was calculated by means of the same method as follows: follow-up for patients who received PRT (n=812) started on the last day of primary RT (according to the definition these patients were at risk for SRT after having received PRT); follow-up for patients who received no PRT (n=1196, of whom 201 patients died within 6 months after diagnosis) started 6 months after diagnosis (by definition patients without PRT were at risk for SRT 6 months after diagnosis). Follow-up of both groups ended on the date of initiating SRT, date of death or 1st January 2005, whichever occurred first. These 2 groups were compared by means of the log-rank test.

Table 2 - Patients receiving secondary radiotherapy (SRT) in a cohort of rectal cancer patients diagnosed between 1996 and 2000 according to stage (except stage unknown), kind of SRT and region

Stage	SRT	Western region	Eastern region
I and II	SRT for LR[a] after PRT[b] on primary tumour	6	6
	SRT for LR without PRT on primary tumour	22	7
	SRT for metastases	13	18
	no SRT	456	502
III	SRT for LR after PRT on primary tumour	7	5
	SRT for LR without PRT on primary tumour	11	10
	SRT for metastases	14	27
	no SRT	153	208
IV	SRT for LR after PRT on primary tumour	3	1
	SRT for LR without PRT on primary tumour	8	2
	SRT for metastases	5	21
	no SRT	120	172

[a]LR=Local relapse
[b]PRT=Primary Radiotherapy

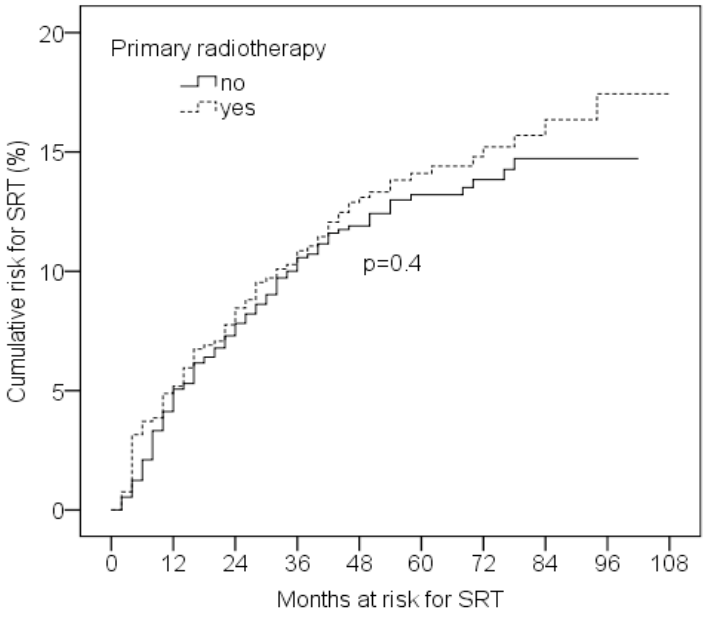
Results

In our cohort of 2008 rectal cancer patients diagnosed between 1st January 1996 and 31st December 2000, 921 patients received RT (63 of whom underwent IORT, 1 patients 2 times) between 1996 and 2005 (median follow-up: 49 months); 718 only PRT, 109 only SRT and 94 both (table 1). In the eastern region 46% of all patients received PRT, in the western region 34%. Six percent of all patients received RT twice or more (94 patients who had received PRT and 23 patients who had received SRT only). The retreat-rate was 20% (187/921).

Secondary radiotherapy

Patients who received SRT were significantly younger and had a higher tumour stage (table 1).

The 203 patients receiving SRT underwent 300 courses, with a range of 1-96 months (median 24 months) after primary diagnosis: 197 courses for metastases and 103 courses for relapsed rectal tumours in 96 patients (90 patients with 1, 5 with 2 and 1 with 3 SRT courses). Thirty-one of these 96 patients received SRT for local recurrence after prior PRT on the rectal tumour, 65 patients received SRT for local recurrence as a first radiation treatment, with a large difference per RT department (table 2). In a multivariate analysis in which only patients with SRT on the rectal recurrence were entered as the dependent variable, the Odds for secondary pelvic irradiation after primary irradiation were 0.7 (95%CI=0.4-1.1); patients with stage III tumours were more likely to receive SRT for a recurrence (OR=2.5, 95%CI=1.4-4.5) and patients in the eastern department significantly less often received SRT for local relapse (OR=0.5, 95%CI=0.3-0.8).



Patients at risk

No PRT:	995	803	701	626	526	369	230	123	43
PRT:	812	615	517	455	392	280	200	117	58

Figure 1: Cumulative use of secondary radiotherapy for patients who received either primary radiotherapy or not in a cohort of rectal cancer patients diagnosed between 1996 and 2000 in South Netherlands. (PTR=primary radiotherapy, SRT=secondary radiotherapy)

Cumulative use of radiotherapy

After 106 months of follow up the cumulative use of RT, either PRT or SRT was 50%. In figure 1 the cumulative use of SRT is shown separately for patients who either received previous PRT or not. The cumulative risk for SRT was 16% at 92 months after start of follow up i.e. after 6 months after diagnosis or after end of primary RT. No significant difference was seen between these 2 groups.

Discussion

To our knowledge this is the first population-based study performed to calculate the total use of radiotherapy in rectal cancer.

We studied the percentage of patients receiving RT as part of their primary treatment (which has been studied extensively in our region[6, 7]), but especially RT as a secondary treatment in a cohort of rectal cancer patients diagnosed between 1996 and 2000, followed until 1st January 2005. In this cohort, 46% of all rectal cancer patients received RT at some point in the course of their illness, which percentage is much lower than the evidence-based estimations from the U.S., Canada and Australia, but it is higher than the actual use of RT in the U.S., Australia and the United Kingdom.[9, 10]

Secondary radiotherapy

Ten percent of all patients in our cohort received SRT, either after previous PRT or more than 6 months after diagnosis without prior PRT. Six percent of the patients received RT two or more times. Acquaintance with RT (as part of the primary treatment) did not significantly influence the total use of SRT or SRT for a recurrent rectal tumour (table 1). Thirty-four percent of all SRT courses were given on a recurrent rectal tumour.

After conventional surgery the local failure rate among patients with rectal cancer amounted to 25-30% without and 10-15% with RT, mostly delivered postoperative.[14] The local recurrence rate after total mesorectal excision (TME), which was applied increasingly during the study period, is 5-15% without and 2-4% with preoperative RT.[14, 15] A loco-regional recurrence of a rectal tumour often leads to major clinical problems including pain, fistulae and bleeding. Even after previous RT a relapsed rectal tumour can be irradiated, sometimes in combination with resection and IORT, with a long-term local control rate of 60-70% after 3 years.[12, 16-18] We considered the combination of external beam irradiation and IORT as one single treatment because it was previously planned as such,[12] and thus affects the planning capacity because IORT equipment must be ready for use in the operating room. Twenty-three percent (n=19) of the planned intraoperative treatments could not be performed.

In the RT department in the eastern part of the region a higher proportion of patients had received PRT because it already started with preoperative RT of 5 x 5 Gray during 1994.[19]

In the other department postoperative RT was largely given for tumours from stage T3 and/or N1 on, and 5 x 5 Gray was exclusively given to patients treated within the framework of the Dutch TME-trial between 1996 and 2000, in which randomisation occurred between total mesorectal excision with or without RT.[1] The cancer registry-based cohort did not contain follow-up data regarding recurrent rectal cancer or metastases. The higher percentage of patients irradiated for a recurrent rectal tumour in the western region (table 2), which also remained after adjusting, may indicate a higher percentage of relapses which might result from the lower use of primary preoperative irradiation in the western region (24% against 77% in the eastern region). Patients with stage III cancer were more likely to undergo SRT for recurrent rectal cancer after adjusting for PRT and region, which indicates a higher relapse percentage for patients with a stage III tumour.

Sixty-six percent of all SRT courses were given to patients with metastases. Skeletal metastases occur in 6-16% of patients with rectal cancer,[20-22] mainly in combination with lung, liver or brain metastases. RT relieves pain in the vast majority of patients with skeletal metastases, but also often relieves symptoms and may prolong median survival for patients with brain metastases.[23, 24]

Cumulative use of radiotherapy

The cumulative risk of receiving RT (PRT or SRT) for our whole cohort amounted to 50% up to 106 months after date of diagnosis. It is not likely that many patients will still be irradiated later. The chance to receive SRT more than 4-5 years after date of diagnosis remains small (figure 1). The cumulative risk to receive SRT is almost the same for patients with or without PRT. Patients who were known in a RT department were not referred earlier or more often than patients who had not been irradiated before.

According to data of the ECR, 65% of all patients with rectal cancer received PRT in 2004. Following the introduction of preoperative RT (5 x 5 Gray) and TME in the whole region in 2001, the rate of locally recurrent rectal cancer is expected to decline, although the rate of distant metastases is not likely to be affected by this change of treatment. We estimate that a total of approximately 69% of all patients with rectal cancer will receive RT with similar indications at some point in the course of their illness, which is comparable with the evidence-based estimations mentioned before.[9, 10] However, the tendency towards a long preoperative chemoradiation regimen of 30 x 1.8 Gray instead of 5 x 5 Gray for patients with a tethered tumour located in the lower part of the rectum,[25, 26] might lower the local recurrence rate further and so decline the need to irradiate on local recurrences. The percentage irradiated patients may be affected by this, but the number of radiation sessions per patient is likely to increase, which has an impact on the RT capacity. Thus the treatment of rectal cancer will remain a dynamic process, influenced by new evidence, and potential changes in clinical view of the oncological community.

Conclusion

The cumulative use of RT in our population-based cohort of rectal cancer was 50% and varied with time and per RT department. The use of SRT on recurrent rectal tumours depended on the difference in primary treatment (i.e. the degree of pre- or postoperative RT) between the 2 RT departments in the region. In the department in the eastern region patients more often received PRT and less often SRT.

Given that cancer treatment is a dynamic process, population-based studies serve to determine the actual use of RT, in order to extrapolate and estimate the future capacity needed for radiotherapy. This study may have contributed to a better comprehension of the total use of RT but especially the use of delayed RT for patients with rectal cancer.

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Chapter 4

Co-morbidity and age

4.1

Influence of age and co-morbidity on receiving radiotherapy as part of primary treatment of cancer in South Netherlands, 1995-2002

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Abstract

Background

To study the influence of age and co-morbidity on receiving radiotherapy (RT) in primary treatment of cancer.

Methods

In a population-based setting we calculated the proportion of irradiated patients within 6 months of diagnosis of lung, rectal, breast and prostate cancer and non-Hodgkin's lymphoma (N=33,369) according to age and co-morbidity between 1995 and 2002. We used logistic regression analysis to adjust for age, co-morbidity, gender, and stage.

Results

Patients with localised non-small cell lung cancer (NSCLC) aged 65 years or older or with co-morbid conditions received RT alone significantly more often compared to younger patients (65-79 years: Odds Ratio (OR)=3.4, 80+: OR=12) or those without co-morbidity (1 co-morbid condition: OR=2.1, 2+: OR=2.4). This also applied for patients with non-localised NSCLC aged 65-79 years compared to younger patients (OR=1.4). RT was administered significantly less often to elderly with resected rectal cancer (65-79 years: OR=0.7, 80+: OR=0.4), with breast cancer after conserving surgery aged 80+ (OR=0.1), and with cT1-cT3 N0 M0 prostate cancer aged 80+ (OR=0.1) than to younger patients. Breast cancer patients undergoing breast-conserving surgery received significantly less often RT in the presence of co-morbidity (1 co-morbid condition: OR=0.6, 2+: OR=0.4). Older patients with aggressive non-Hodgkin's lymphoma received RT as only treatment significantly more often compared to younger patients (OR=3.4).

Conclusion

Co-morbidity and age did have influence on receiving RT, although for most tumour types age appeared to be a stronger predicting factor. Under-treatment was found for patients with breast cancer or rectal cancer.

Introduction

Serious co-morbidity is present in more than 50% of cancer patients aged 60 years and older.[1, 2] The highest prevalence is found for patients with lung, kidney, stomach, bladder and prostate cancer (between 50 and 60%). For patients with serious co-morbidity, the standard oncological treatment might be altered because of an increased risk of complications or a limited life expectancy due to non-oncological reasons. Also, for elderly patients therapy is often less aggressive due to fragility or alleged increased toxicity.[3] Because elderly patients are less easily comparable due to an often unique combination of diseases, it is not clear when a modification of treatment would be justified. This is also reflected by the fact that in general elderly patients are excluded from clinical trials. It is therefore more complex to choose the optimal treatment for elderly patients or for patients with co-morbid conditions. Several authors have reported that older patients receive radiotherapy (RT) less often.[4-6] Adjuvant RT after surgery might be withheld. On the other hand, RT is sometimes a good alternative for surgery or chemotherapy (CT), e.g. in the case of localised prostate cancer.

We studied the influence of age and co-morbidity on receiving RT in the primary treatment of cancer in South Netherlands in the period 1995-2002.

Table 1 - Classification of co-morbidity, according to an adapted version of the Charlson Co-morbidity Score (1987)[9]

Previous malignancies (except basal skin carcinoma and carcinoma in situ of the cervix)
Chronic Obstructive Pulmonary Diseases (COPD)
Cardiovascular diseases (myocardial infarction, cardiac decompensation, angina pectoris, intermittent claudication, abdominal aneurysm, peripheral arterial disease)
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Hypertension
Diabetes mellitus
Digestive tract diseases (gastric diseases, Crohn's disease, ulcerative colitis, liver cirrhosis, hepatitis)
Other (connective tissue diseases, severe rheumatoid arthritis, kidney diseases, dementia, tuberculosis, chronic infections)

Methods

The Eindhoven Cancer Registry, which covers a large part of South Netherlands with approximately 2.4 million inhabitants, records data on all patients newly diagnosed with cancer since 1955. This population-based registry is supported by six pathology departments, hospital medical records offices in 10 general hospitals and two large, but accessible, RT departments to which the distance for patients is less than one hour of travel.

Table 2 - Age-specific prevalence (%) of the most common serious concomitant diseases[a] among newly diagnosed cancer patients amenable to radiotherapy in South Netherlands, 1995-2002[2]

		Any co-morbidity (%)			Previous cancers (%)			Heart & vascular disease (%)			COPD (%)			Hypertension (%)			Diabetes mellitus (%)		
Tumour type		age 50-64 years	age 65-79 years	age ≥80 years	age 50-64 years	age 65-79 years	age ≥80 years	age 50-64 years	age 65-79 years	age ≥80 years	age 50-64 years	age 65-79 years	age ≥80 years	age 50-64 years	age 65-79 years	age ≥80 years	age 50-64 years	age 65-79 years	age ≥80 years
Lung	Male	53	74	72	9	16	16	18	34	32	20	24	31	11	15	11	7	10	11
	Female	49	67	61	9	16	14	11	22	25	21	24	16	12	21	22	6	12	11
Colorectal	Male	40	64	71	7	15	22	13	28	32	6	15	15	16	21	15	7	10	13
	Female	37	56	65	10	14	16	5	14	24	5	8	9	15	25	25	5	14	17
Prostate	Male	36	56	59	6	9	14	12	24	27	5	12	15	12	17	12	4	8	9
Breast	Female	28	52	67	6	10	15	4	12	22	4	6	8	13	29	27	5	13	16
NHL	Male	39	67	76	5	14	19	13	27	39	4	15	11	13	17	16	5	9	11
	Female	32	61	65	5	16	13	5	11	23	2	8	4	14	26	20	6	12	13

[a] more than one condition per patient possible

COPD = Chronic Obstructive Pulmonary Disease, NHL = non-Hodgkin's lymphoma

Registration takes place via the hospital charts 6 to 18 months after diagnosis by trained registrars. Recorded are patient characteristics (such as age, gender), tumour characteristics (e.g. localisation, morphology (according to the International Classification of Diseases for Oncology[7]) and stage (according to the Tumour-Node-Metastasis (TNM) system 5th edition[8])) and primary treatment (planned within 6 months of diagnosis). Since 1993 serious co-morbidity with prognostic impact has also been recorded via the medical records for all patients according to a slightly modified version of the Charlson co-morbidity index.[9] Within the framework of the cancer registry it was not feasible to register severity of co-morbidity. However we only recorded serious co-morbid conditions with possible prognostic impact, except for hypertension (table 1). Despite the lack of access to death certificates, the infrastructure of and good access to Dutch health care facilities, together with the notification procedures used, have resulted in cancer registries with a completeness exceeding 95%.[10]

Our study population consisted of 33,369 newly diagnosed cancer patients aged 50 years or older with lung (N=8946), colorectal (N=8540, of which 3058 with rectal cancer), breast (N=8097), or prostate cancer (N=6326) or non-Hodgkin's lymphoma (NHL) (N=1460) diagnosed between 1995 and 2002, all tumours amenable to RT.

The prevalence of co-morbidity, according to age and tumour type, was based on data from the Cancer Registry. Completeness and accuracy of the data on co-morbidity were validated in random samples of different tumour sites (internal reports). Co-morbidity was scored correctly in 80-90% of patients. However, there was some under-registration, mainly of cardiovascular diseases. Therefore, the real effects of co-morbidity are possibly stronger than those presented in this study. For each tumour type the proportion that received RT (including adjuvant RT) and the proportion receiving other therapies such as surgery, CT, hormonal therapy, 'other treatments' and no therapy, were computed according to age and the number of co-morbid conditions (0, 1 and 2 or more). 'Other treatments' included: treatment for metastases (if applicable), hormonal only (breast), immune therapy, therapy not otherwise specified, laser therapy, photodynamic therapy (lung), RT alone (rectal), high-dose CT before stem cell therapy (breast, NHL), bone marrow transplantation (breast, NHL), peripheral stem cell therapy (breast, NHL), transurethral tumour resection (prostate) or splenectomy (NHL). Patients with lung cancer were divided into patients with non-small cell lung cancer (NSCLC) stage I (T1-T2 N0/X M0/X) and II (T1-2 N1 M0/X or T3 N0/X M0/X), NSCLC stage III (T1-2 N2 M0/X, T3 N1-2 M0/X, any T N3 M0/X or T4 any N M0/X) and limited (confined to one hemithorax, including hilar ipsilateral and contralateral mediastinal and supraclavicular lymph nodes) small cell lung cancer (SCLC). Patients with NSCLC stage IV (any T any N M1) and extensive (any disease beyond limited) SCLC were excluded. Patients with NHL were subdivided into indolent versus aggressive lymphoma according to the REAL classification by recoding the registry data, which were originally recorded according to the Working Formulation.[11] Age groups were 50-64, 65-79 and 80 years or older for rectal, lung, breast and prostate cancer, and 50-69 and 70 years or older for NHL because of the small numbers of patients.

Differences between age groups were tested with the chi-square test. Logistic regression analysis to determine the independent effects of age, co-morbidity, gender, stage and grade (for breast and prostate cancer) on receiving RT or RT and CT was applied to subgroups of the following tumour types: lung cancer (stage I and II NSCLC combined, stage III NSCLC and limited SCLC), rectal cancer (stage I-III (any T any N M0), resected), breast cancer (after breast-conserving surgery), prostate cancer (cT1-cT3 N0 M0) and aggressive and indolent NHL.

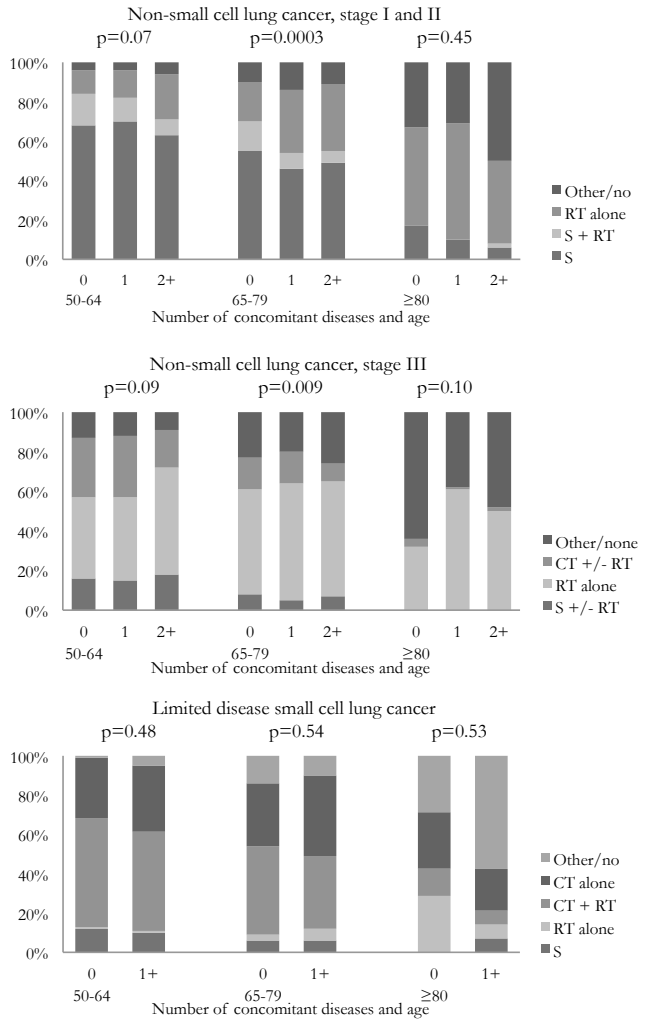

Figure 1: Primary treatment of lung cancer in South Netherlands, 1995-2002, according to age and concomitant diseases. RT = radiotherapy, CT = chemotherapy, S = surgery

Results

The prevalence of co-morbidity increased with age (p<0.0001). The lowest prevalence was found for patients with breast cancer, the highest for patients with lung cancer (p<0.0001) (table 2).

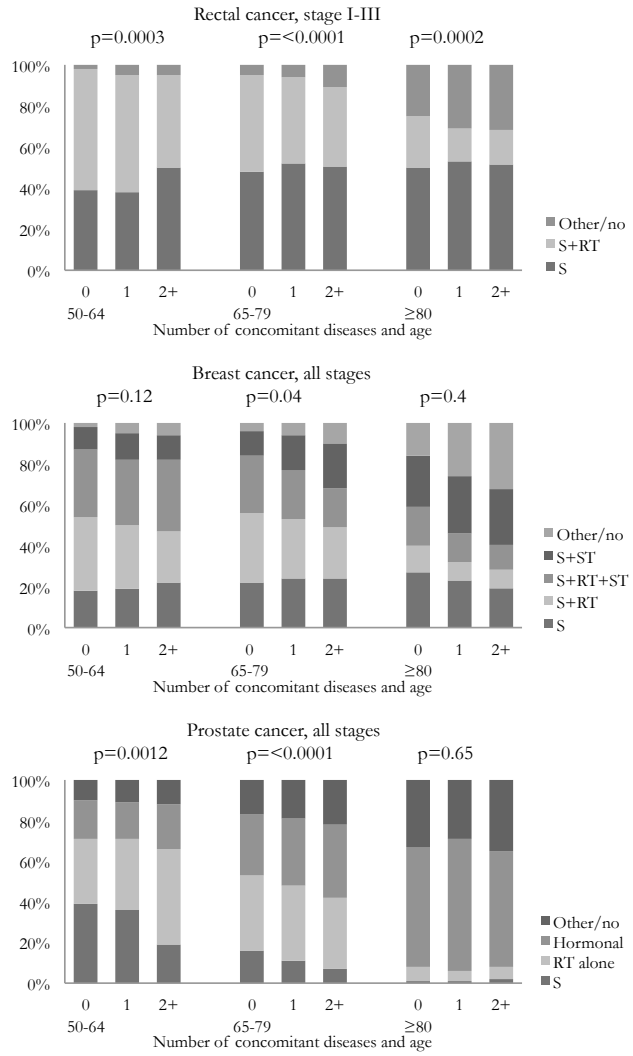

Figure 2: Primary treatment of rectal (stage I-III), breast and prostate cancer in South Netherlands, 1995-2002, according to age and concomitant diseases. RT = radiotherapy, ST = systemic therapy, S = surgery

A higher proportion of elderly patients (65+) with *lung cancer* received RT as single therapy (figure 1). For patients with stage I and II NSCLC aged 80 years or older RT was the most frequently used treatment modality, in contrast to surgery for younger patients.

Eighty-four percent of the patients with other/no therapy did not get oncological treatment. Younger patients with stage III NSCLC received CT with or without RT more often, while patients aged 80 years or older received only RT or other/no therapy. Of all patients with other/no therapy 67% received no treatment. Patients aged 80 or older with limited SCLC received RT alone more often instead of a combination of CT and RT. Ninety-six percent in the category other/no therapy were not treated. The logistic regression analysis showed that higher age (65+) was an independent factor for RT as a single therapy for each tumour type, except for patients aged 80 years or older with NSCLC stage III (table 3).

In contrast, elderly patients with rectal cancer stage I-III, breast cancer or prostate cancer received RT less often (figure 2). Although 60% of the patients with *rectal cancer* aged 80 or older underwent surgery, adjuvant RT was often withheld. Fifty-four percent of the patients with other/no treatment were not treated. Patients with stage I-III rectal cancer received pre- or postoperative RT less often if they were 65 years or older (table 3).

Elderly patients with *breast cancer* underwent surgery less often than younger patients, and after surgery older patients received RT less often. Twenty percent of all patients with other/no therapy were not treated, 80% received mostly hormonal therapy (figure 2). After breast-conserving surgery patients aged 80 or older received RT significantly less often (Odds Ratio = 0.1, 95% Confidence Interval = 0.1-0.2) (table 3).

Patients aged 80 years or older with *prostate cancer* seldom received RT. Most patients in this group received hormonal or other/no (of which 88% no treatment) therapy (table 3).

Patients aged 70 or older with *aggressive NHL* received RT more often as a single therapy compared to those younger than 70 years, but received CT combined with RT less often (table 3). Sixty-one percent of the patients with other/no therapy were not treated (figure 3). No difference was seen between patients younger than 70 years and those aged 70 or older with *indolent NHL* who received only RT (figure 3) or CT combined with RT (table 3). Seventy-nine percent of the patients with other/no therapy received no treatment.

Patients with stage I and II *NSCLC* suffering from concomitant diseases received RT as single therapy significantly more often (table 3).

The number of co-morbid conditions did not significantly influence the proportion receiving RT among patients with resected *rectal cancer* stage I-III.

For patients with *breast cancer* treated with breast-conserving surgery the chance of receiving adjuvant RT was significantly lower when 1 or more concomitant diseases were present (table 3).

According to regression analysis the chance of receiving RT for patients with cT1-cT3 N0 M0 *prostate cancer* was not significantly different for patients with or without concomitant diseases.

Patients with *aggressive NHL* with concomitant diseases received RT in combination with CT less often (table 3).

Table 3. - Chance to receive primary radiotherapy according to age and concomitant diseases in South Netherlands, 1995-2002

Tumour type	Age (years)	OR*	95%CI	p-value	Number of concomitant diseases	OR¶	95%CI	p-value
NSCLC, stage I and II, only	50-64	1			0	1		
RT	65-79	3.4	2.3-4.8	<0.0001	1	2.1	1.4-3.0	0.0003
	≥80	12	7.4-19.7	<0.0001	2+	2.4	1.6-3.5	<0.0001
NSCLC, stage III, only RT	50-64	1			0	1		
	65-79	1.4	1.1-1.7	0.003	1	1.2	1.0-1.5	0.07
	≥80	1.1	0.7-1.6	0.8	2+	1.2	1.0-1.5	0.11
Limited SCLC, RT after CT	50-64	1			0	1		
	65-79	0.7	0.5-1.1	0.08	1+	0.9	0.6-1.3	0.7
	≥80	0.4	0.1-1.7	0.4				
Limited SCLC, only RT	50-64	1			0	1		
	65-79	6	1.4-28.7	0.02	1+	1.1	0.4-3.4	0.6
	≥80	17	3.0-118.6	0.002				
Rectal cancer stage I-III,	50-64	1			0	1		
RT after surgery	65-79	0.7	0.5-0.8	0.0004	1	1	0.8-1.3	0.9
	≥80	0.4	0.3-0.6	<0.0001	2+	0.9	0.7-1.1	0.2
Breast cancer, RT after	50-64	1			0	1		
breast-conserving surgery	65-79	0.9	0.6-1.3	0.5	1	0.6	0.4-0.8	0.0002
	≥80	0.1	0.1-0.2	<0.0001	2+	0.4	0.3-0.7	<0.0001
Prostate cancer	50-64	1			0	1		
cT1-cT3, N0, M0, only RT	65-79	1.1	0.9-1.3	0.3	1	1.1	0.9-1.2	0.5
	≥80	0.1	0.1-0.2	<0.0001	2+	1.1	0.9-1.3	0.4
Non-Hodgkin's lymphoma	<70	1			0	1		
aggressive, only RT	≥70	3.4	1.3-5.9	<0.0001	1+	0.9	0.8-1.1	0.3
Non-Hodgkin's lymphoma	<70	1			0	1		
aggressive, CT and RT	≥70	0.5	0.4-0.8	0.002	1+	0.6	0.5-0.8	0.02
Non-Hodgkin's lymphoma	<70	1			0	1		
indolent, only RT	≥70	1.1	0.6-2.0	0.9	1+	0.8	0.7-1.0	0.08
Non-Hodgkin's lymphoma	<70	1			0	1		
indolent, CT and RT	≥70	0.6	0.3-2.0	0.3	1+	1.9	0.9-4.3	0.2

OR=odds ratio, 95%CI=95% confidence interval, NSCLC=non-small cell lung cancer, SCLC=small cell lung cancer RT=radiotherapy, CT=chemotherapy, cT1-cT3=clinical tumour classification
*adjusted for co-morbidity, gender and stage
¶adjusted for age, gender and stage

Discussion

In this study we found that older age was a stronger factor for receiving RT than the presence of co-morbid conditions. With increasing age and/or the presence of concomitant diseases RT substituted other more aggressive therapies (lung cancer and NHL), but adjuvant RT was withheld more often from older patients with tumours for which surgery is recommended (rectal and breast cancer).

The higher prevalence of co-morbidity among older cancer patients was not unexpected (table 2) and might even be underestimated due to an ascertainment bias. In general, younger patients underwent surgery or CT more often. Therefore, the prevalence of co-morbidity scored by the treating physician might be higher among younger patients, due to the screening examinations required before surgical or systemic treatment.[2, 12]

Co-morbid conditions may complicate radiation treatment due to a higher range of late toxicity.[13] Because of the higher frequency of co-morbidity among the elderly, being old tends to be confused with being chronically ill. Also the general attitude of doctors is likely to be influenced by the belief that tolerance for treatment might be compromised among older patients or that the course of cancer might be less aggressive.[14] However RT can be highly effective for many cancer types and is well tolerated by even very old patients (80+).[15-17] On the other hand: for elderly patients there may be several other reasons why they should not endure RT, such as the distance to the RT department and the sometimes protracted RT course. Frailty, functional disability, social support, psychological or economical factors and the patient's or family preference can also influence treatment decisions.[18] So maybe it is not abnormal for older patients to receive therapies other than the standard therapy.

Older patients with *NSCLC* stage I and II are often high risk operative candidates because of poor cardiac or pulmonary condition. For such patients RT with a curative intent can and should be offered as an alternative to surgery.[19, 20] Our study is in agreement with this treatment policy. A high proportion of elderly patients with *NSCLC* stage III received no or only supportive treatment,[21] although even high-dose radiation therapy is well tolerated by the elderly.[22-24] Elderly patients and patients with co-morbid conditions usually received RT as a single therapy, while younger patients underwent CT, either with or without RT, more often. In a retrospective study from Canada it was also found that older patients and patients with increased co-morbidity with *limited SCLC* were less likely to receive a combination of CT and RT.[25]

Resection of the tumour is the recommended curative treatment for *rectal cancer*. Randomised trials show an improvement in local control with postoperative or preoperative RT.[26, 27] Also for older patients treatment decisions should be based on the available data.[28] In our study older patients were treated with a combination of surgery and RT less often, as in other population-based studies.[29-32] We found no influence of co-morbidity on the use of adjuvant RT for patients with a resected rectal tumour, stage I-III. On the other hand, some studies described a slight negative influence,[29-31] but the populations studied were not the same with regard to stage. In an in-depth study of 455 randomly selected rectal cancer patients stage I-III from our study population, a higher complication rate was found for patients aged 70 years and older, patients with co-morbidity and patients treated with the combination of surgery and RT.[33]

The low percentage of RT among older *breast cancer* patients or patients with co-morbid conditions can partly be explained by withholding adjuvant RT after breast-conserving surgery, as reported elsewhere.[34-37]

However, the local failure rate increases with time of follow up for (also elderly) patients who have undergone a lumpectomy or segmental resection only, in contrast to those who were also irradiated.[38, 39]

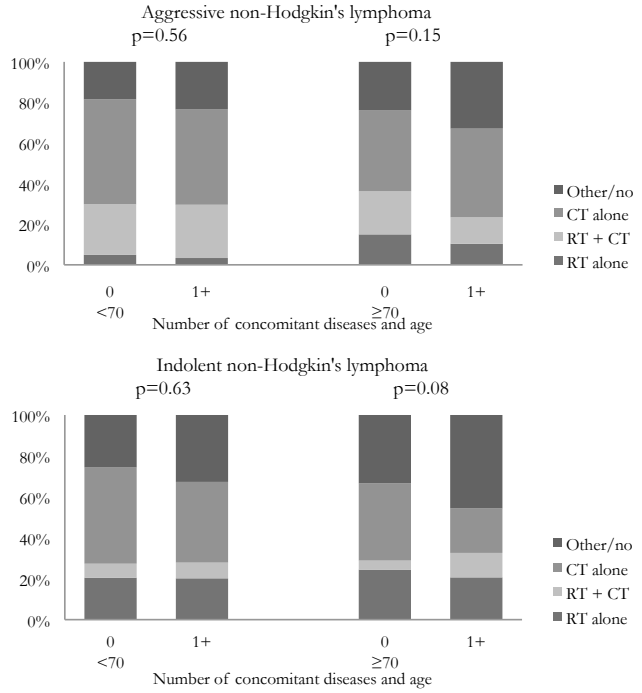

Figure 3: Primary treatment of non-Hodgkin's lymphoma in South Netherlands, 1995-2002, according to age and concomitant diseases. RT = radiotherapy, CT = chemotherapy

A retrospective analysis of elderly women treated with breast-conserving surgery from Pennsylvania (USA) showed that breast carcinomas were not indolent and should be treated optimally.[40] In 2 randomised prospective trials in older patients RT plus tamoxifen significantly reduced the risk of locoregional recurrence, compared to tamoxifen alone.[41, 42]

Another explanation for the low proportion of RT may be more mastectomies without RT among elderly patients, in discordance with the guidelines.[12, 43, 44] Women in British Columbia (Canada) of 70 years or older had a similar or higher chance of recurrence after mastectomy without RT compared to younger women.[45] In our study we also found a rather high proportion of other treatments or even no therapy for elderly patients. A case control study by the Geneva cancer registry reported that nearly 50% of women aged 80 years or older received suboptimal treatment.[46] A higher RT-related complication rate was not found for elderly patients in a descriptive study from Texas (USA).[47] On the contrary, complications following RT were more prevalent among patients younger than 70 years in a randomly sampled selection of 527 patients from our study population.[12]

Other authors also found that older patients with *prostate cancer* received RT less often.[48] Potentially curative therapy (surgery or RT) might lead to significant gains in health outcomes for men up to at least 75 or 80 years with moderately or poorly differentiated localised prostate cancer.[49]

U.S. national surveys of prostate cancer showed similar treatment outcomes after RT for patients aged younger than 70 and those aged 70 or older.[50] In a prospective study from Mississippi (USA) it was found that patients undergoing radical prostatectomy had significantly less co-morbidity than those undergoing RT.[51] We found no significant influence of co-morbidity on the chance to receive RT.

A combination of (reduced dose) chemotherapy and involved field radiation therapy for stage I and II aggressive *NHL* was found to be safe, highly effective and potentially curative for the elderly,[52-54] with or without concomitant diseases.[55] In our study elderly patients received RT alone more often, very likely due to the fact that RT offers a good alternative for these patients.[56]

The treatment of patients with early stage indolent follicular lymphoma is local RT, for patients with advanced stage CT or watchful waiting (low-burden disease).[57] We found no influence of co-morbidity or age (table 3).

Older age appeared in our study to be a stronger factor affecting the receipt of RT than the presence of co-morbidity. For elderly patients or patients with co-morbid conditions RT was substituted for more aggressive, surgical or systemic, therapy (lung cancer and NHL). Adjuvant RT was often withheld before or after surgery (rectal and breast cancer), which may lead to higher recurrence rates for which the time to develop seems long enough with an average life expectancy of 15 respectively 8.5 years for a 70 or 80 year old Dutch woman and 12, respectively 6.5 years for a man of the same age according to Statistics Netherlands.[58]

So, in principle, adjuvant radiotherapy should still be offered to elderly patients with breast or rectal cancer, unless the benefits become too small by short life-expectancy or serious complications can be expected. This pertains to patients after breast-conserving surgery,[59] after mastectomy with high grade disease and in resectable rectal cancer patients stage II and III.[27, 28]

Although for men aged 80+ with prostate cancer a 'wait and see' policy seems appropriate for asymptomatic and low-risk tumours, other patients should receive curative radiotherapy or hormonal therapy.

Older patients with NSCLC stage I or II should also receive surgery, after careful selection, whereby curative RT can be an alternative[60] in case of a high surgical risk. Patients with NSCLC stage III with a good performance score can be treated optimally by a combination of CT and RT. RT alone is an alternative for patients who are at a high risk of CT-related complications. The rule should thus be to follow guidelines and standards unless.

To learn more about treatment outcome and complications in older patients or patients with serious co-morbid conditions, prospective studies are needed, and the reason for exclusion should be reported as well.

The potential harm of withholding RT from these patients with respect to recurrences, survival or quality of life can also be studied in existing databases.

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4.2

Should radiotherapy be avoided or delivered differently in elderly patients with rectal cancer?

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Abstract

Purpose is to give an overview of treatment possibilities of rectal cancer over time, but also of the real management of rectal cancer especially in relation to age. From literature search representative randomised studies on patients with resectable rectal cancer, comparing only surgery, post- and preoperative radiotherapy with or without chemotherapy, are reviewed. We also reviewed the literature regarding radiotherapy for rectal cancer described in population-based studies.

The overview of the trials showed that preoperative radiotherapy improves local control in relation to no or postoperative radiotherapy. Adding chemotherapy did not significantly improve survival. No relations were seen between age and complications. All population-based studies showed that increasing age is associated with less (neo)adjuvant treatment.

To avoid local recurrence, the best possible treatment, being preoperative RT, should be given to all patients with resectable rectal cancer, irrespective of age.

Introduction

In literature there is no clear definition of 'elderly' patients. It is however important to realize that 80% of all patients with rectal cancer is over the age of 60 years, 50% over the age of 70 years and 20% over the age of 80 years. The only treatment modality in rectal cancer for cure is radical (pathological negative tumour margins) surgery. The aim of (neo)adjuvant treatment is the reduction of local recurrences and the improvement of survival. A number of trials assessed the use of either pre- or postoperative radiotherapy (RT). Preoperative RT has the advantage of intact anatomy (vasculature) and good oxygenation of the tumour cells. Well oxygenated tumour cells are more susceptible for irradiation than relative hypoxic cells. Depending on whether a short (e.g. 5 x 5 Gray (Gy)) or long irradiation course is given, devitalisation or downsizing/downstaging of the tumour can occur. Disadvantages of preoperative RT are that all tumours are irradiated and thus over-treatment may occur for low-staged tumours. Furthermore in case of a long course of preoperative irradiation exact pathological staging is not possible anymore.

The main advantage of postoperative RT is the selection of patients who may benefit of adjuvant treatment on the basis of pathological tumour staging, thus avoiding over-treatment. Disadvantages of postoperative RT are the relative hypoxia in the operated area making tumour cells less susceptible for irradiation and the small bowel that will be in the irradiation fields causing acute and late toxicity.

Although survival is the most important endpoint of any cancer treatment, especially in rectal cancer the avoidance of a local recurrence, causing a very negative impact on the quality of life, is of utmost importance. Meta-analyses[1, 2] show that postoperative RT has no impact on survival while preoperative RT is reported to have a significant, be it modest, positive effect. Both post- and preoperative RT reduce the local recurrence rate significantly, preoperative RT being more effective than postoperative RT. We give an overview of the treatment possibilities of rectal cancer over time. However, since population-based studies provide insight in the real management of patients with rectal cancer especially in relation to age, this issue will be addressed separately.

Methods

In preparation of the national Dutch guidelines for peri-operative RT for rectal cancer, an extensive literature research was performed in (inter)national guideline databases, websites of oncology societies, Medline, Embase etc., for reviews, controlled randomised trials etc. in order to establish the role of peri-operative RT with or without chemotherapy (CT) for today's clinical practice. From these results a representative number of reviews and trials over the last two decades is shown to highlight the evolution to the present status of peri-operative RT.

We also reviewed the literature regarding RT for rectal cancer described in population-based studies. For this a computerised search of the literature was performed in Pubmed with the terms population-based, radiotherapy and rectal neoplasm.

The reference lists of all identified publications were checked to retrieve other relevant publications, which were not identified by means of the computerised search. With the above mentioned search we identified 22 publications, of which hard copies were obtained. Studies were included if they described, in a population-based setting, RT use or RT use in combination with CT in relation to age. We limited our search to English, German and Dutch language studies.

Results

The selected trials are described hereafter in chronological order and are summarised in table 1. Four of these trials used no age-limitation during the randomisation.

Two Scandinavian studies, the Stockholm study[3] and SRCT study,[4-6] comparing surgery versus surgery and a short course of preoperative RT (5 x 5 Gy in 1 week), showed a significant reduction of the local recurrence rates in favour of the irradiated patients. Due to the large irradiation fields (up to L2) and the irradiation techniques (2 opposing fields) there was an 8% postoperative mortality rate in the irradiated group in the Stockholm trial. This mortality excess disappeared when irradiation was limited to the small pelvis and multiple field technique was used as in the SRCT trial. Cancer specific survival was significantly improved in both trials. Perineal wound healing problems were seen significantly more in the irradiated group especially when the perineum was included in the irradiation fields and an abdominal perineal resection had been performed. Another Scandinavian study,[7, 8] the only one in the world until now comparing a short course of preoperative RT with postoperative RT, showed a significant reduction in local recurrence rate in favour of the preoperative short course; survival was not significantly different. The patients in the preoperative irradiated group had significantly more perineal wound healing problems (acute toxicity). Small bowel obstructions as well as grade 3 toxicity occurred more often in the postoperative irradiated group (late toxicity). Noteworthy was the fact that 50% of the patients could not start their postoperative treatment within 6 weeks of operation.

In 1991 Krook and colleagues[9] published the results of a study comparing postoperative RT alone with postoperative RT and CT. Local recurrence and distant metastases rates were significantly reduced in the combined modality arm; survival was significantly improved in the combined modality arm. Toxicity was comparable between both arms. The Dutch TME trial[10-15] comparing total mesorectal excision (TME) versus a short course of preoperative RT (5 x 5 Gy in 1 week) followed by TME within one week, showed a significantly lower 5-year local recurrence rate for the irradiation arm. Survival was the same. Perineal wound healing disturbances (acute toxicity) and bowel dysfunction (late toxicity) were seen significantly more in the irradiated group. Sauer and colleagues[16] published in 2004 the results of a German study comparing preoperative CT-RT versus postoperative CT-RT. The local recurrence rate was lower for patients treated preoperative with CT-RT; survival was the same. Both acute and late toxicity were significantly increased in the postoperative treated group.

Table 1 - Nine randomised studies comparing different treatment modalities in patients with resectable rectal cancer

Study	Authors	Number of patients	Age limit	Year start trial	Year results	Treatment-arms	Local recurrence rate	Survival
Stockholm study	SRC Study group[3]	849	no upper age imit	1980	1990	S versus RT (5x5 Gy) + S	4 year: 23% versus 11%, p ≤ 0.01	4 year: 50% versus 60%, p = 0.05
Swed. rectal cancer trial	Folkesson et al[4-6]	1168	< 80	1987	2005	S versus RT (5x5 Gy) + S	13 year: 26% versus 9%, p ≤ 0.001	13 year: 62% versus 72%, p = 0.03
Upsala trial	Frykholm et al[7,8]	471	no upper age limit	1980	1990	S + RT (60 Gy) versus RT (5x5 Gy) + S	5 year: 22% vs 13 %, p = 0.02	5 year: NS
USA	Krook et al[9]	204	no upper age limit	1980	1991	S + RT (45-50 Gy) versus S + RT (45-50 Gy) + CT	7 year: 25% versus 13.5%, p = 0.04	7 year: 48% versus 57%, p = 0.03
TME	Kapiteijn et al[10-15]	1861	no upper age limit	1996	2005	S (TME) versus RT (5x5 Gy) + S (TME)	5 year: 11% versus 6%, p = 0.001	5 year: NS
Germany	Sauer et al[16]	823	<75	1994	2004	S + CT + RT (50 Gy) versus CT + RT (50 Gy) + S	5 year: 13% versus 6%, p = 0.006	5 year: NS
EORTC 22921	Bosset et al[17]	1011	<80	1993	2005	RT (45 Gy) + S versus CT + RT (45 Gy) + S versus RT (45 Gy) + S + CT versus CT + RT (45 Gy) + S + CT	5 year: 17% versus 9% versus 10% versus 8%, p = 0.002	5 year: NS
FFCD 9203	Gerard et al[18]	733	<75	1993	2005	RT (45 Gy) + S + CT versus RT (45 Gy) + CT + S + CT	5-year: 16.5% versus 8 %, p = 0.003	5 year: NS
Poland	Bujko et al[19]	312	<75	1999	2006	RT (5x5 Gy) + S versus RT (50 Gy) + CT + S	NS	NS

SRC=Stockholm Rectal Cancer, Swed.=Swedish, RT=radiotherapy, CT=chemotherapy, S=surgery, Gy=Gray, NS=not significant

Furthermore ± 50% of the patients treated postoperative did not receive full course irradiation or CT. The EORTC 22921 study,[17] comparing long course preoperative RT versus preoperative CT-RT versus preoperative RT followed by postoperative CT versus preoperative CT-RT followed by postoperative CT, described a significant difference in local recurrence rates in favour of the CT-arms; survival was the same. Similar results were reported from the French FFCD 9203 study[18] comparing preoperative RT versus preoperative CT-RT, both arms followed by adjuvant CT. Bujko and colleagues reported in a randomised trial comparing preoperative short-course RT with preoperative conventionally fractionated CT-RT no differences in survival, local control nor late toxicity.[19]

In contrast with clinical studies, population-based studies are the best way to assess the management of a disease in daily practice. We found 10 population-based studies (described below, summarised in table 2), all published after 1999, describing the management of patients with rectal cancer in relation to age. Most studies examined the relationship between patient characteristics, among which age, and the use of adjuvant (pre- or postoperative) RT or RT and CT. However this was not always the only endpoint.

Paszat and colleagues described the use of surgery for rectal cancer and the subsequent risk of permanent colostomy. Patients older than 80 years were less often irradiated after resection without colostomy in relation to younger patients.[20] Schrag and colleagues examined the relationship between patient characteristics and the use of RT with and without CT among patients aged 65 years or older with stage II and III rectal cancer. The chance to receive RT (mostly postoperative) or RT combined with CT was significantly lower for patients older than 69 years of age.[21] Schroen and colleagues identified patient, hospital and surgeon characteristics associated with variation in treatment. The compliance for RT in stage II and III was 73% for patients younger than 60 years of age and only 25% for patients aged 75 years or older. After adjusting, patients aged 60 years or younger received 9.5 times more often a combination of surgery, RT and chemotherapy for stage II and III rectal cancer than patients aged 76 or older.[22] Dharma-Wardene and colleagues also found that elderly patients (≥75 yr) received multimodality therapy less often than younger patients; they also described a risk of death 2.35 higher for patients aged 75 or older receiving surgery only with respect to elderly patients undergoing surgery plus multimodality therapy.[23] In the study of Neugut and colleagues an increasing age was associated with a decreased probability of adjuvant treatment with RT and CT. Combined RT and CT was associated with improved survival for stage III rectal cancer.[24] Ayanian and colleagues found a significantly lower chance to receive RT for patients older than 75 years of age. The lack of clinical efficacy was cited by physicians as the most common reason for not administering radiation therapy to patients with rectal cancer, followed by patient refusal and co-morbidity.[25] Phelip and colleagues described a shift from postoperative RT in 1990 into preoperative RT in 1995, when 72% of all irradiated patients received preoperative RT. Patients aged 75 or older were given adjuvant RT half as often as younger patients, and major geographical differences were observed.[26, 27]

Table 2 - Population-based studies describing radiotherapy or radiotherapy and chemotherapy for resectable rectal cancer in relation to age

Author Study period	Purpose	No. of patients	Stage and age inclusion	Percentage RT	Multivariate analyses
Paszat et al[20] 1982-1994	To describe the use of surgery and RT for newly diagnosed rectal cancer patients and the subsequent risk of permanent colostomy	18695	All stages, all ages	1982: 5%, 1994: 22%	Odds for RT after resection without colostomy: (ref=60-69) 70-79=0.6, ≥80=0.2 (all sign)
Schrag et al[21] 1992-1996	To examine the relationship between patient characteristics and the use of RT with and without CT among patients aged 65 and older with stage II and III rectal cancer	1670	II and III, >65 years	Total: 57%; 65-69: 73%, 70-74: 66%, 75-79: 52%, 80-84: 39%, ≥85: 21%"	Odds for RT: (ref=65-69) 70-74=0.7, 75-79=0.4, 80-84=0.2, ≥85=0.1 (all sign)
Schroen et al[22] 1994-1996	To assess the use of surgical procedures and adjuvant therapy in the initial treatment of rectal cancer and to indentify patient, hospital and surgeon characteristics associated with variation in treatment	637	All stages, all ages	Total: 37%. stage I: 14%, stage II: 53%, stage III: 63%, stage IV: 30%	Odds for S, RT, CT in stage II and III: (ref=≥76) 70-75=4.2, 60-69=4, <59=9.5 (all sign)
Dharma-Wardene et al[23] 1991-1998	To describe relationship between age and treatment, to compare risk of death in elderly (≥75 years) receiving optimal (S + RT +CT) regimen with those who received surgery only, and to compare 5-year survival for each treatment group	1979, random sub-sample of 259	All stages, all ages	Total: 59%	Univariate: elderly (≥75) less often multimodality treatment (p=0.0001)
Neugut et al[24] 1992-1996	To investigate the use of treatment with CT and RT among patients over 65 years with surgically resected stage II or III rectal cancer	1807	II and III, >65 years	Total: 48%. 65-69: 66%; 70-74: 55%; 75-79: 47%; 80-84: 34%; ≥85: 17%	Odds for RT+CT: (ref=65-69) stage II: 75-79=0.4, 80-84=0.3, ≥85=0.07. Stage III: 70-74=0.4, 75-79=0.25, 80-84=0.1, ≥85=0.04 (all sign, p-trend=<0.01)
Ayanian et al[25] 1996-1997	To estimate underreporting of adjuvant therapies in routinely collected registry data, assess rates of adjuvant therapy and factors associated with use, and ascertain why eligible patients were not treated	1956	II and III, >18 years	<55: 82%, 55-64: 76%, 65-74: 68%, 75-84: 47%, ≥85: 14%	Odds for RT: (ref=65-74) 75-84=0.3, ≥85=0.1. Odds for RT+CT: <55=2.7, 75-84=0.3, ≥85=0.1 (all sign)
Phelip et al[27] 1995	To determine whether diagnostic and therapeutic management practices for rectal cancer vary in different geographic regions	683	All stages, all ages	Total: 47%	Odds for RT: (ref=<75) ≥75=0.47 (sign)
Phelip et al[26] 1990 and 1995	To evaluate how the results of a consensus conference (1994) were taken into account	1990: 402, 1995: 543	All stages, all ages	1990: 42%, 1995: 47%	Odds for preop RT: (ref=<75) ≥75=0.67 (sign)
Baxter et al[28] 1976-2000	To evaluate US trends in adjuvant RT over 25-year, timing of RT and factors affecting RT	45000	All stages, >18 years	Total: 32%; 1976: 12%, 2000: 42%	Odds for RT in stage II and III: (ref=>70) 65-70=3, ≤60=5 (all sign)
Vulto et al[29] 1995-2002	To study the influence of age (and co-morbidity) on primary RT	3058	I-III, >50 years		Odds for RT: (ref=50-64) 65-79=0.7, ≥80=0.4 (all sign)

RT = radiotherapy, CT = chemotherapy, S = surgery, ref = reference category, sign = significant

In the USA an increase was seen in adjuvant RT from 1976 to 2000, with a shift into preoperative RT from 1996; patients who underwent RT were younger than those who did not undergo RT, also in multivariate models.[28] Also in our own region we found a significantly lower use of RT for elderly patients.[29]

Discussion

All population-based studies showed that increasing age is associated with less (neo)adjuvant treatment. Also other authors described this phenomenon.[30-32]

The fear that elderly patients do not tolerate radical pelvic RT as well as young patients is not substantiated in the study by Pignon and colleagues;[33] they conclude that age per se is not a limiting factor. Also doctors' or patients' preference, co-morbidity or frailty, socio-economic factors or fear for toxicity may play a role. Shahir and colleagues described an almost 2 fold higher complication risk within one year after diagnosis for patients who underwent surgery and RT, and for patients aged 70 years or older, but no association was made between age and RT.[34]

Increased postoperative mortality, mainly among elderly patients, was described in two studies, in which a short course of preoperative RT was given in large irradiated pelvic fields.[2, 3, 35] All other randomised studies we described, used other RT techniques with smaller tissue volumes. In these studies no relations were seen between age and complications, so it is tempting to believe that a large irradiated volume may be deleterious in the older age group.

At this moment staging (by imaging), preoperative treatment and TME-surgery are cornerstones in the treatment of rectal cancer. The choice however between a short preoperative RT course or a long preoperative CT-RT course is made difficult by lack of exact definitions of 'early', 'mobile', 'resectable' and 'locally advanced' rectal cancer. Due to the overlap of tumour stages between these groups there is a risk of under- or over-treatment. We consider T4 tumours and tumours with a margin less than 2 mm to the perirectal fascia on MRI as 'locally advanced'. In recent years, the value of MRI for reliable prediction of the circumferential resection margin has been established. In single institution studies it was demonstrated that it allows accurate assessment of the circumferential resection margin and by that the choice for optimal therapy. A recent publication of the Mercury study confirmed the reliability of MRI in a multicenter setting. Therefore, MRI should now be considered as standard of care in the preoperative work-up for rectal cancer patients.[36] N2 tumours can be considered as 'locally advanced' also, but the problem is the clinical determination of the N2 status. The issue of sphincter-saving surgery after long preoperative chemo-radiotherapy has not been solved yet.

Given the lack of improvement of survival in trials using long course preoperative CT-RT the question remains whether CT should be added to reduce the local recurrence rate considering the results of the short course preoperative RT trials. We believe that, when no downsizing/-staging is needed, 5 x 5 Gy followed by TME within one week of completion of RT is the treatment of choice.

If the tumour is located more than 10 cm. above the anal verge omission of RT may be considered. In case of locally advanced tumours a long course of preoperative CT-RT followed by operation approximately 6 weeks later (in order to achieve downsizing/-staging) is necessary. Depending on the patient's status a short course of preoperative RT like 13 x 3 Gy with operation 6-8 weeks later (Lyon R90-01 trial)[37] or even 5 x 5 Gy followed by surgery after more than 4 weeks can be considered (Bujko[19] or ongoing Stockholm-III trial). As pointed out by Rutten and colleagues in this EJC issue[38] future studies may focus on delayed TME surgery after a short course of preoperative RT, in order to reduce the hazard of double trauma by RT and surgery. For more locally advanced tumours the role of local excision after preoperative treatment or even chemo-radiotherapy alone and omitting surgery in order to reduce the risk of surgical trauma, may be explored.[38, 39]

Conclusion

Preoperative (chemo)-radiotherapy improves local control in rectal cancer. No differences were seen in toxicity between young and elderly patients when modern RT techniques with small tissue volumes are used. To avoid local recurrence, the best possible treatment should be given to all patients with resectable rectal cancer, irrespective of age: a short preoperative RT course for patients with a primary resectable tumour, a long course of preoperative CT-RT for patients with locally advanced tumours. Exceptions should be made only for patients who are unable to fulfil the combination treatment because of patients' condition.

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Chapter 5

Palliative radiotherapy

5.1

General practitioners and referral for palliative radiotherapy: a population-based survey

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Submitted for publication

Abstract

Because of the suspicion that the referral rate for palliative radiotherapy (RT) is too low, we sent a questionnaire to all general practitioners (GP) to evaluate the knowledge of palliative RT among GP's in the south of the Netherlands. Four hundred and ninety-eight of the 1100 questionnaires were analysed. Forty-six percent of the respondents had cared for patients referred for palliative RT in the last 2 years. Knowledge about the effects of palliative RT on bone metastases and spinal cord compression was good but moderate to poor about other palliative indications. Determinants of the actual referral for palliative RT were mainly patient-related. GP's considered their own knowledge to be poor with only 10% reporting previous RT education. It is absolutely necessary to inform GP's about the possibility of short series of palliative irradiation in order to improve their information for symptomatic cancer patients about all possibilities for palliative treatment.

Introduction

In the Netherlands general practitioners (GP) provide primary care for an average of 2350 inhabitants. In general, for more complex and specialised care, GP's refer their patients to second line specialists, who, if necessary, refer to 3rd line specialists such as radiation oncologists.

GP's increasingly provide day-to-day home-bound care for cancer patients who need palliation.[1] The number of such patients has increased substantially over the last decades because of the growing incidence of cancer in the ageing population in the Netherlands[2] and the trend that people prefer to spend the last phase of their life in their own environment. Radiotherapy (RT), especially a short series, is an essential and established modality within palliative care, for example for localised symptoms including painful bone metastases, spinal cord compression, brain metastases or airway obstruction due to a vena cava superior syndrome.[3, 4] Samant and colleagues (Ontario-Canada) evaluated the knowledge of GP's about the indications for palliative RT and factors that affect patient referral by means of a survey.[5] Many GP's appeared to be unaware of the effectiveness of RT for a variety of common palliative situations, and RT referral could be correlated with knowledge about indications for palliative RT.

Earlier studies[6, 7] of the pattern of care showed a marked variation in secondary or delayed RT for breast and rectal cancer, suggesting differences in the referral of such patients with metastases or recurrence, while the higher referral for patients with spinal cord compression on Fridays[8] illustrated deficiencies in clinical awareness also among GP's. We thus thought it worthwhile to evaluate knowledge of palliative RT and factors which influence referral for palliative RT among general practitioners.

Methods

We developed a questionnaire, based on the Canadian survey.[5] Because GP's are often the medical care-takers in the last 3 months of the life of cancer patients, we concentrated only on palliative RT given in this terminal phase. The questionnaire included the following sections: respondent characteristics, number of patients in the palliative-terminal phase and number of patients referred for palliative RT, factors influencing referral for palliative RT, perception of the effectiveness of palliative and symptomatic RT, former education and willingness to learn more about palliative RT. The questionnaire was tested on GP's attending a peer group course on palliative care.[9] After a few adaptations the survey consisted of 23 questions. The completion time was less than 15 minutes.

In January 2007 the survey was sent to all GP's (n=1140) within the area of the Comprehensive Cancer Centre South and a small adjacent region in the west, together covering about 2.6 million inhabitants. This region is supported by general hospitals only and two large radiotherapy departments, one in the western and one in the eastern part of the region; most patients live within 30 minutes distance and never have to travel more than one hour for RT.

Some patients might be referred to a RT Department outside the region, closer to their home. The completed surveys were collected and analysed. Forty questionnaires could not be delivered because the physician's address was no longer applicable. The survey response was 503 out of 1100, but 2 surveys arrived after the results had been processed, yielding a response rate of 45.5%. Three questionnaires were not valid because only one or no items were filled in. So we had 498 (45.2%) surveys for our analyses. If we assume that in each GP Health Centre 2 or 3 GP's work and only 1 GP returned the survey, then, assuming that all GP's follow the same policy, we could re-calculate the response rate to be between 58.2 and 71.2%.

Table 1 - Profile of the responding general practitioners

	Respondents (n=498)		All GP's[b] in the Netherlands[a]
	number	%	%
Gender			
Male	375	75.3	65
Female	122	24.5	35
Not reported	1	0.2	
Year of graduation as GP[b]			
1970-79	145	29.1	17
1980-89	184	36.9	36
1990-94	66	13.3	11
1995-99	61	12.2	14
2000-2006	41	8.2	22
Not reported	1	0.2	
Type of practice			
Solo	153	30.7	20
Association	190	38.2	30
Health Centre	143	28.7	50
HIDHA[c]	9	1.8	
Not reported	3	0.6	
Working days per week			
3 days or less	111	22.3	25
4 days	120	24.1	*
Fulltime	265	53.2	*75
Unknown	2	0.4	
Distance to RT[d] Department			
< 30 minutes	196	39.4	
30 to 60 minutes	281	56.4	
> 60 minutes	21	4.2	

[a]NIVEL=Netherlands Institute for health services research[10]
[b]GP= General Practitioner
[c]HIDHA=GP employed by an independently working GP
[d]RT= Radiotherapy
*Considered full time by NIVEL

Results

The characteristics of the responding GP's are shown in table 1. The office of ninety-five percent of all physicians was located less than one hour from an RT Department, 77% said their patients were treated in one of the 2 RT Departments in the region, 23% in RT Departments in adjacent regions (Rotterdam, Utrecht, Nijmegen, Heerlen-Maastricht). Almost all GP's who completed the survey (96%) considered themselves to be the most important care-giver of terminal patients who received palliation. Most physicians (57%) indicated caring for 1-5 terminal patients per year and 31% for 5-10. Forty-seven percent said they had ever referred patients directly for palliative RT, 36% of whom more than once in the last two years. Fifty percent of the responding physicians referred patients after consulting a second-line specialist.

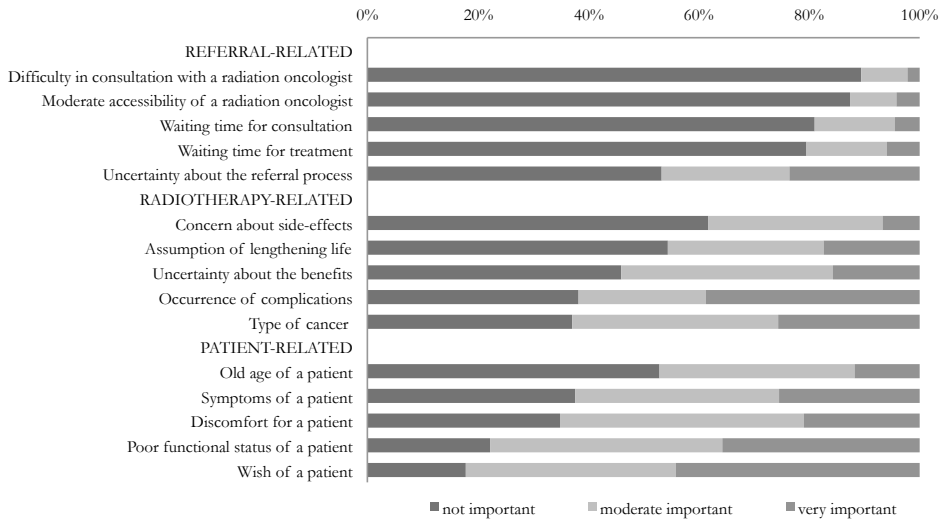

Figure 1: Proportional distribution of determinants that have a negative influence on the decision by general practitioners to refer a patient in the palliative-terminal phase for palliative radiotherapy

The most important negative factors affecting referral for palliative RT were general condition, presumed discomfort and wish of the patient. RT-dependent factors, such as accessibility of a radiation oncologist, were found to have little influence (figure 1). For one-third of the respondents, life expectancy did not seem important for referral for palliative RT, whereas 42% considered a minimum life expectancy of 6 weeks to be essential.

Most responding physicians considered RT effective for painful bone metastases, spinal cord compression, painful local disease, brain metastases and airway obstruction.

The potential effectiveness for managing haemoptysis and haematuria was not as well recognised (figure 2).

About 40% of the respondents assessed their own knowledge of RT as modest, including their knowledge about the application and benefit of short series of palliative RT. Knowledge about possible side effects and their management was reported by 56% and 43%, respectively. Time since graduation as GP did not seem to affect these figures. However, only 4% of the physicians who graduated in the seventies had received education in palliative care, in contrast to 78% of those who graduated after 2000. All together, only 10% of all GP's received education in palliative RT, either during their training for GP or post-academically. Ninety-five percent of all responding physicians would consider attending courses in palliative RT.

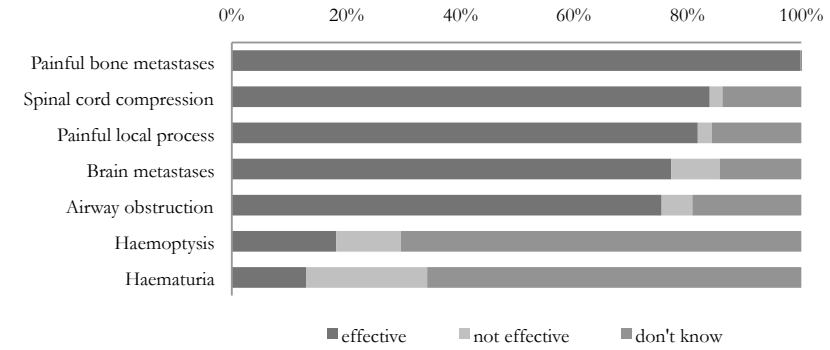

Figure 2: Cancer-related symptoms and appraisal by general practitioners of the effectiveness of palliative radiotherapy

Discussion

In the south of the Netherlands almost all of the responding general practitioners appeared to be actively involved in the care of cancer patients in the terminal phase of their disease.

The profile of the responding GP's was roughly comparable with the profile of all Dutch GP's, as registered by NIVEL (Netherlands Institute for health services research)[10] (table 1), with some overrepresentation of older, male physicians working alone and under-representation of young physicians.[11] Some under-representation of GP's working in a health centre seems likely since often only one GP per centre responded.

Earlier studies reported the presence of five to six terminal cancer patients in a median GP practice; 31% of the GP's in this survey indicated that they cared for a somewhat higher number of patients in need of palliation. Furthermore, almost all of them considered themselves to be the most important care-giver, while earlier studies reported GP's to be the most important care-giver for only two patients out of five to six terminal patients.[12, 13]

According to the radiation oncologist most patients are referred by specialists such as surgeons and oncologists, whereas 47% of the responding GP's indicated that at some time they had referred patients directly for palliative RT.

We assume that the responding GP's meant that the patients were referred indirectly for palliative RT, by specialists to whom the GP referred. Furthermore, while GP's only have about 5 terminal patients per year, they might have a different experience with referral patterns than radiation oncologists who see many patients. Moreover there might have been some 'socially desirable' answers.

Patient-related characteristics such as discomfort and poor condition (but not age) affected the decision to refer for palliative RT. Most important, GP's indicated that they reacted to the wish of the patient, partly because they were not sufficiently aware of the possibilities of palliative RT to relieve symptoms. This might be a consequence of the low percentage who received education in palliative RT.

Despite the rather low appraisal of their own knowledge about palliative RT, the responding GP's seem well-informed about the effectiveness of symptomatic RT for painful bone metastases.[14] Furthermore, knowledge about the treatment of spinal cord compression seems to be sufficient, which is very important for the chances of restoration of neurological function.[8, 15]

Almost half of our respondents mentioned a minimal life expectancy of six weeks as a parameter for referral for palliative RT, which is in agreement with the average time to response after a single fraction for painful bone metastasis, being about three weeks;[16] however 30% indicated that life expectancy was not a criterion.

Conclusion

Most of the respondents considered their own knowledge about (palliative) RT and potential side effects as modest, which might have led to fewer referrals for palliative RT for cancer patients. Special education in palliative RT and (treatment of) side effects, desired by almost all responding GP's, might give them more insight into the possibilities of palliative RT for haematuria, haemoptysis, airway obstruction, brain metastases, painful local processes and spinal cord compression as well as more tools to inform the patients properly.

A (desired) side-effect of the questionnaire is likely to be an increased awareness of the possibilities of palliative RT among (responding and non-responding) GP's and therefore more appropriate referral.

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5.2

Always on a Friday? Time pattern of referral for spinal cord compression

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Acta Oncologica 2001; 40: 88-91

Abstract

For patients with spinal cord compression, radiotherapy should be initiated as soon as possible to optimise the chances for restoration of neurological function. The speed of referral in the region of our radiotherapy institution with 9 general hospitals was analysed based on a tumour and treatment related registry. From January 1987 to December 1997, 443 patients were treated. All patients were seen and treated on the day of referral. Significantly more referrals took place on Friday, 30%, compared to 12% on Monday, 17% on Tuesday, 15% on Wednesday, 20% on Thursday, 5% on Saturday and 1% on Sunday ($p<0.002$). This difference was the same for patients who were formerly treated in our institution ($n=242$) or not ($n=201$). No significant difference was found between different categories of patients ($p=0.28$). These data are discussed with referring physicians to encourage speed of diagnosis and referral.

Introduction

Metastatic disease to the bone often affects the vertebral bodies, with the most affected sub-site the lumbar spine while the most common site for spinal cord compression secondary to metastatic disease is the thoracic spine.[1-3] The underlying primary cancers most frequently reported are breast, lung, and prostate.

Pain is the most common presenting symptom of vertebral metastases. Most patients presenting with metastatic spinal cord compression have endured back pain for weeks. Radicular pain in the arms, in the legs, or across the chest is an important prodromal symptom.[4] Myelopathy, radiculopathy, or cauda equina syndrome are all possible. A particular important sign is loss of proprioception and sphincter function. This is a harbinger of serious neurologic damage and is much less likely to recover following any form of treatment. Sensory levels, if present, may be numerous segments lower than the level of the compression. Paraplegia usually means cord infarction which is irreversible.

The differential diagnosis includes benign neoplasms, herniated intervertebral discs and infectious syndromes. Some of the early signs and symptoms can also be caused by other metastatic locations such as brain metastases or by tumoural compression of peripheral nerves. Especially when a patient with myelopathy or neuropathy does not have associated back pain that preceded the neurologic dysfunction, a cause other than metastasis to the epidural space must be considered.

Table 1 - Primary tumour sites of 'old' patients, already known at our department and 'new' patients who come for the first time at our department

	'Old' patients		'New' patients	
	n	%	n	%
Breast	84	35	14	7
Lung	49	20	33	16
Prostate	48	20	46	23
Renal	10	4	15	8
Stomach/colorectal	10	4	11	6
Unknown primary	7	3	51	25
Myeloma	3	1	12	6
Other	31	13	19	9
Total	242	100	201	100

MRI is the most informative study for the evaluation of the patient with suspected metastasis involving the epidural space. The extent of vertebral bony metastasis and the number of epidural compressions can be evaluated in one single study.[5] MRI demonstrates more than one epidural tumour in 20% of the referred patients. Patients who cannot undergo a MRI should be offered a myelography, if necessary complemented with a CT scan.

The standard of practice in past years was to perform an emergency posterior operative procedure, followed by postoperative irradiation.

Retrospective studies, confirmed by a randomised trial of radiation versus laminectomy and posterior decompression of the spinal cord, demonstrated that radiation therapy without surgery is as successful as surgery plus irradiation in ambulatory patients and in paretic patients who respond to steroids.[6-10] An operative procedure including decompression of the spinal cord, tumour debulking and stabilisation of the affected vertebrae, can be considered for fracture dislocation, since patients with spinal instability, retropulsed bone fragments, or complete collapse of the vertebral body with myelopathy rarely benefit from irradiation alone. A surgical intervention should be considered also if no histologic diagnosis of cancer has been made, in case of rapid progression and serious neurological deficiency, in radioresistant tumours and in an earlier irradiated anatomical location.

After diagnosis, a starting dose of 10 to 20 mg of dexamethasone or an equivalent dose of another steroid, followed by 12 to 16 mg in 3 to 4 times a day, relieves pain and improves neurologic symptoms in most patients.[11] Especially if the neurologic deficit has improved with steroid therapy, patients are likely to benefit from irradiation. Patients are maintained on steroids, and dose tapering occurs gradually after the completion of irradiation. Many radiation dose-time relations have been used, without difference in outcome: 20 to 30 Gray in 5 to 10 fractions in 1 to 2 weeks, given with a simple treatment technique.[7, 12-14]

In general, survival is limited after the diagnosis of cord compression with ambulation as the most important pre-treatment factor for response and the most important post-treatment factor for survival. Patients ambulatory after treatment have a median survival time of 8 to 12 months, compared to 1 month for non-ambulatory patients.[12, 15-20] Other prognostic factors are the anatomic location of metastases, functional status and primary tumour histology. The medial survival time of patients with favourable tumour types (lymphomas, myelomas, or hormone-sensitive malignancies as breast and prostate) was 12 months, whereas for patients with unfavourable types it was 4 months.[21] An associated vertebral compression fracture of more than 50% yielded a poor response.

Since quick and adequate treatment is important for the quality of life, any delay should be avoided as much as possible. However, in our institution for radiotherapy, working in close collaboration with 9 general hospitals, the opinion existed that these patients did have a delay in referral with most referrals on a Friday. Many other radiation oncologists working in other institutions, in the Netherlands as well as in other countries, share this feeling. However, this time pattern has, to our knowledge, not formerly been studied. The purpose of this study was to investigate the referral pattern by retrospectively analysing the first day of radiation treatment.

Material and methods

Based on a tumour and treatment-related registry, an analysis of referral for urgent radiotherapy for spinal cord compression was retrospectively performed. From January 1987 to December 1997, 443 patients were treated urgently with a combination of steroids and radiotherapy. All patients were seen and started their treatment on the same day on which referral took place.

Depending on the time period, a total dose of 20 to 30 Gy was given in 5 to 8 fractions with the first 3 fractions without a break, thus if necessary including the weekend.

'Old' patients (n=242) are defined as patients formerly seen and treated at our department. We divided 'new' patients (n=201) into patients with a known primary tumour but not formerly seen in our institution (n=77) and patients in whom no primary tumour was known or with spinal cord compression diagnosed within the first month after diagnosis of their malignant disease (n=124).

One-way Anova (Analysis of Variance) and Duncan's Multiple Range test were performed on this data to investigate differences. A two-tailed t-test was used to analyse differences between groups. 95% confidence intervals were calculated.[22]

Results

Table 1 shows the distribution of the site of the primary tumour for 'old' and 'new' patients. In 'old' patients, breast, lung and prostate are the most frequent primary tumours, together representing 75% of the referred patients. Unknown primary site, prostate and lung are most frequently seen in 'new' patients, accounting for a total of 64% of the referred patients in this category.

Table 2 - Number of patients referred on respective days of the week. No significant difference between patient categories was found. A two-tailed t-test was used to analyse differences between groups. Numbers are in absolute values

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Total
'Old'	27	39	36	55	68	14	3	242
'New', known	12	14	11	11	27	2	0	77
'New', unknown	12	21	18	23	39	8	3	124
All	51	74	65	89	134	24	6	443

In table 2 the distribution of referral throughout the days of the week is displayed. For all categories of patients, significantly more referrals took place on a Friday as compared to other days of the week: 30% versus 12 – 20%. Only few referrals took place during the weekend, respectively 5% on Saturday and only 1% on Sunday. There is no significant difference between any combination of the three patient categories ($p=0.24$ to 0.56). Figure 1 shows the frequency distribution for all patients together. The difference between Friday and the other days of the week is significant ($p<0.002$) with even a trend of an inclining referral from Monday to Friday. Referral during the weekend is very rare.

Discussion

In a study of patients with spinal cord compression in a general hospital, Stark and colleagues note that lung cancer was responsible in 33%, breast cancer in 28%, other identifiable sites in 25%, and unknown primaries in 14% of the cases.[23]

In our series, lung cancer was less common (19%), and we identified prostate cancer (21%) as the second most common primary tumour site, immediately behind breast cancer (22%). Unknown primaries represented a comparable 13%. Neurologic symptoms due to spinal metastases occurring as the first evidence of malignant disease was reported by Stark in 47% of 131 patients, in contrast to only 28% in our series of patients referred for urgent radiotherapy. Our lower rate can be explained by selective referral of patients without a known primary tumour for neurosurgery to obtain material for histological diagnosis.

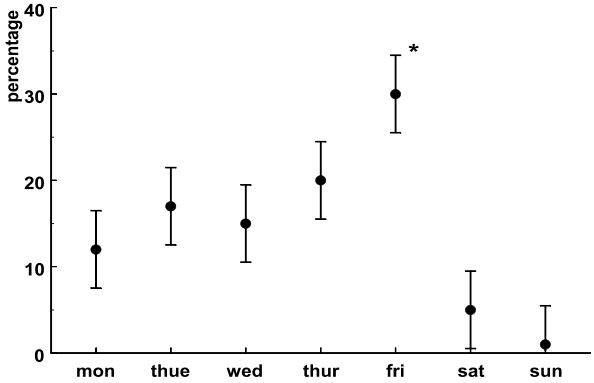

Figure 1: Percentage of patients referred on respective days plotted as mean with 95% confidence intervals. * Statistically significant difference from other days of the week ($p < 0.002$, ANOVA test)

Since the initial neurological function status is one of the most important predictors for recovery after treatment, any delay in the diagnostic procedure and the initiation of radiotherapy might have a negative impact on the chance of recovery from the neurological syndrome. Diagnosis of spinal cord compression should and can be made within hours after the moment that a patient presents with signs and symptoms. After clinical neurological examination, a MRI has to be made urgently with referral for radiotherapy within 24 hours after the moment that the patient came for medical assistance. The first 2 to 3 fractions have to be given on consecutive days, thus if necessary also on Saturday and/or Sunday.

In our series of 443 consecutive patients, significantly more referrals (almost one third) took place on a Friday ($p<0.002$), with only a very low referral rate during the weekend. Theoretically, referral would have to be distributed evenly over all days of the week. Since it is not possible to foresee already on Friday referrals of patients with spinal cord compression who would present normally during the weekend, a peak on Friday indicates that most diagnoses and referrals are made in the second half of the week, indicating a delay in this process.

A number of possible reasons can be imagined for introducing such a delay: the patient or his family might postpone seeking medical advice; the family doctor might not be familiar with this disease; the specialist whom the patient is referred to might underestimate the signs and symptoms and not realise the negative effect of any delay; MRI-facilities are not everywhere and anytime easily available and finally, the radiotherapy department might not be prepared to treat these patients during all hours of the week. Since most of these possible reasons introducing a delay do not differ from one day in the week to another, an important aspect of the concentration of referrals on Fridays could be the effect of the weekend to come with patients, family and physicians trying to avoid medical problems in those days. In part based on this idea, many clinical departments have their 'large clinical visits' at the ward on Friday.

The also noted lower referral rate during the weekend can not entirely be explained by a patient's and doctor's delay during the weekend since this would result in a higher referral rate on Monday, which is not the case. It might be interpreted as a supplementary argument that the process of diagnosis and referral takes often several days.

Remarkably, no significant difference in pattern of referral was found between 'old' and 'new' patients ($p=0.28$). This means that in our series neither the medical history of the patient nor the fact that a patient had or had not been seen before in our institution, had an influence on the speed of diagnosis and referral.

Because of the negative impact of the delay of treatment on the chance of recovery from the neurological syndrome, measures should be taken to avoid this. Our data are discussed with referring physicians and have been presented at a scientific meeting of the local comprehensive cancer centre in order to encourage speed of diagnosis and referral. Patients at risk for spinal cord compression are made aware of the importance of possible neurological signs and symptoms to stimulate them to seek early medical advice. Registration of the time pattern of referral will be continued and reported prospectively.

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Chapter 6

General discussion

General discussion

Trends

This thesis gives an overview of the use of radiotherapy from 1988 to 2006 in an increasing and ageing population in the south of the Netherlands, a region served only by community hospitals and 2 large radiotherapy institutes (with no differences in geographical and socio-economical background of the target population) to which travel distances are on average 30 minutes with a maximum of one hour for 10% of the target population. We did not study the influence of travel time on receiving radiotherapy. Jones and colleagues (northern England) found that the likelihood of receiving radiotherapy was reduced with increasing travel time to the nearest radiotherapy facility.[1] The total number of patients who were irradiated increased with 3.3% a year, because of the increasing number of newly diagnosed cancer patients.[2] The proportion primarily irradiated patients remained stable, although a shift was seen in indications for radiotherapy for different tumour groups. There appeared to be an increase for rectal[3] and prostate cancer patients[4] and a decrease for lung[5] and gynaecological[6] cancer patients; for the latter, however, an increase was seen in the period 2003-2006, probably because of the implementation of new guidelines for endometrial and cervical cancer in 2004.[7] About 31% of all cancer patients in the region of the Comprehensive Cancer Centre South and registered in the Eindhoven Cancer Registry received radiotherapy as part of their primary treatment. In the western part of the region about 29% was irradiated, in the demographically similar eastern part of the region a slightly higher proportion of 32% was found, mainly due to a higher proportion irradiated patients with breast, rectal and prostate cancer.[8] This difference between the 2 regions has not been reduced during the latter years up till 2006.

Waiting-times for radiotherapy became longer in the Netherlands during the late 90's, but never unacceptable, also because of excess-increase demand related to mass-mammography and opportunistic prostate screening. From 2002 a descent in waiting-times was achieved, according to the benchmark of the Dutch association of Radiotherapy (NVRO),[9] also because of increase of equipment and personnel.

Variations in referral

Taking age and stage at diagnosis into account, variations in referral for radiotherapy between regions and hospitals usually result from differences in referral behaviour of individual specialists. Because radiotherapy is a third line treatment, patients must be referred by second line specialists (or and rarely, by first line general practitioners in case of palliative treatment). It seems that, despite the presence of guidelines and wide efforts at implementation through the professional societies and regional comprehensive cancer centres, some specialists do not seem to be in full agreement with them, while also consultants from the University Hospitals might have influence. However, in medicine there are always rapid and slow adapters as appeared in the implementation of a short preoperative radiation course with operable rectal cancer in chapter 3.2.

Furthermore, variations can develop by differences in assessment of side effects of radiotherapy or differences in assessment of short- or long-term complications: omitting adjuvant radiotherapy might result in more local recurrences, but these recurrences might be easier to treat, although local recurrences might also be instrumental in the development of distant metastases.[10] So, to a certain extent variation in application of adjuvant therapy might also reflect incomplete knowledge.

This same phenomenon might be seen in elderly patients with breast, rectal and prostate cancer: the lower radiotherapy rates for these patients were seen both in the eastern and in the western region; the rates are increasing in the latter years in the eastern region, especially for breast and rectal cancer.

Individual specialists might have their own expectations and appraisal about acute reactions and late complications. Variations in referral rates between them might become smaller if they are informed more systematically about side effects of the latest irradiation schedules,[11-13] which might often occur only occasionally and thus not well known or only among radiation oncologists. They should be studied in a prospective way and regularly communicated by journals which are relevant for referring specialists.

In contrary to the Scandinavian and Anglo-Saxon countries where the medical oncologists are responsible for both systemic treatment and radiotherapy, in the Netherlands the medical oncologists, second-line specialists, only are responsible for systemic treatment. Adjuvant radiotherapy, a third-line specialism, might therefore have more competition from systemic treatment.

Population-based studies and estimated optimal utilisation studies

In Australia a model of radiotherapy utilisation was developed by the radiotherapy society between 2003 and 2005 to estimate the maximal and optimal utilisation of radiotherapy for the whole country. According to this model 52% of all cancer patients should receive radiotherapy at least once at some time during the course of their illness.[14] For breast cancer patients (excluding ductal carcinoma in situ) the estimation was that 86% of all patients should at least have an indication for radiotherapy once during the course of their illness, for rectal cancer patients 61%.[15, 16] These estimates have been based on the hierarchy of levels of evidence for indications for radiotherapy as used by the Australian National Health and Medical Research Council, and epidemiological data on the proportion of patients who would qualify for radiotherapy. The actual radiotherapy utilisation rates in Australia were much lower than the estimated rates, possibly partly because of the large distances there. A prospective survey of radiotherapy (curative and palliative) practice in 2001 in Sweden showed comparable percentages of actual use as found with the Australian model.[17]

Population-based trend studies, as discussed in chapter 2.1 and 2.3, only give insight in radiotherapy rates for primary treatment (which can be curative or palliative).

Population-based cohort studies can give a true insight in the whole spectrum of radiotherapy consumption.

As described in chapter 3.1 and 3.2 of this thesis, the cumulative use of radiotherapy for patients with breast cancer in the south of the Netherlands was 67%, and for patients with rectal cancer 50%. The following explanations can be given for the discrepancies between real management, as in our studies, and the tumour-specific estimations from the Australian model.

At first, we found a significantly lower radiotherapy use for elderly patients with breast and rectal cancer during their primary treatment (chapter 4.1), but also for secondary treatment for recurrences or metastases (chapter 3.1 and 3.2). Also patients with co-morbid diseases were irradiated less often, as we found among breast cancer patients (chapter 4.1). The levels of evidence in the Australian model were mostly from randomised trials, in which elderly patients and patients with co-morbidity often not are included.

Secondly, the adherence of guidelines differs with referring specialists so they might not refer all patients for radiotherapy who are eligible.

Thirdly, especially for breast cancer, the median follow-up time of our cohort may be too short (66 months, range 0-107); the majority of recurrences and distant relapses occur in the first 5 years after diagnosis, but breast cancer often behaves as a chronic disease. Although the life expectancy of breast cancer patients has become similar to the general female population 20 years after diagnosis, the risk of dying from breast cancer remains elevated.[18] Therefore patients can receive a first (palliative) radiation treatment many years after the first appearance of the disease. In our cohort only 28% of the patients had died on 1st January 2005, so the cumulative use of radiotherapy may increase slowly after that time with 1% a year.

Radiotherapy use versus referral

In this thesis we only studied the actual use of radiotherapy. Patients who were referred, but not treated, were not registered as such in the Eindhoven Cancer Registry. A study from Ontario showed that most of the decline in the rate of radiotherapy use with age, particularly for adjuvant and palliative indications, was related to a decline in referral to the cancer centres, not to a refusal of the radiation oncologist.[19] In our population-based studies we also found a significant lower use of adjuvant and palliative radiotherapy for elderly patients, which, most plausibly, is the result of a lower referral rate by treating specialists.

Age and co-morbidity

Elderly patients with cancer, especially patients with breast, rectal and prostate cancer, received less often radiotherapy, as we saw in chapter 2, 3 and 4.

For patients with breast[20] and rectal cancer (chapter 4.2) the low radiotherapy rates in elderly patients are common and often a result of omitting pre- or postoperative radiotherapy.

Breast cancer patients, also elderly, with a resectable tumour can safely undergo breast-conserving surgery in combination with radiotherapy.[21, 22]

Elderly patients, however, tend to receive often surgery alone, without irradiation,[23] which results in an at least 3 to 4 fold increased risk of local recurrences[24] within 5 to 10 years. Although elderly patients more often receive a mastectomy,[23] probably to avoid a long course of irradiation, this will not automatically prevent the need for postoperative radiotherapy.[7, 25] Post-mastectomy radiotherapy has been shown to reduce the frequency of loco-regional recurrences by 70%, also in elderly women and irrespective of the use of adjuvant systemic treatment.[26-28] Moreover, in combination with systemic treatment radiotherapy seems more effective as well, resulting in a higher reduction of the recurrence risk, as has been suggested by some.[27]

An alternative might be to give adjuvant hormonal treatment to the subset of patients with hormonal sensitive tumours.[24, 29] However, the local recurrence risk seems to increase at longer follow up[29] and side effects and therapy compliance have to be taken into account as well.

A significant percentage of patients aged 80 or older received no surgery at all (chapter 4.1), which might strongly decrease the ultimate prognosis.[30] Indeed women at the age of 80 nowadays have a median life expectancy of 8.5 years.[31]

In operable rectal cancer radiotherapy plays an important role in the prevention of local recurrences (at first postoperative, but this changed in the mid 90's to nowadays nearly always preoperative[32]). However, preoperative radiotherapy tends to increase the risk of developing complications which may influence the referral in elderly patients and in patients with co-morbidities.[33, 34]

For localised prostate cancer the detection rates increased after the widespread introduction of the PSA-test since 1994.[35] It might increase even more because the ageing of the male population. The lack of randomised, prospective trials hampers any comparison of the efficacy of different treatment modalities, surgery and radiotherapy.[4] However, encouraging results are achieved in several trials evaluating radiotherapy and adjuvant hormonal treatment for, also elderly, patients with locally advanced tumours.[36, 37] Also, especially in elderly patients or in patients with co-morbid conditions, active surveillance may be a reasonable approach, resulting in a low percentage of elderly patients being treated immediately after diagnosis.

To gain a better insight in reasons why elderly patients are less treated with radiotherapy, reasons for excluding (with an indication of life expectancy) should be reported prospectively. Moreover, prospective studies are warranted to learn more about treatment outcomes and complications in older patients, and in patients with serious co-morbid conditions.

Palliative radiotherapy

Although radiotherapy is a third line treatment, general practitioners can refer patients (probably only those who have been irradiated before) directly for palliative treatment of metastases, which might be very convenient because of less travel movements[38] and less loss of time.

However, the survey, which we sent to all general practitioners in the region of the Comprehensive Cancer Centre South to evaluate knowledge of and influencing factors for palliative radiotherapy, showed that about half of the respondent general practitioners assessed their own knowledge of palliative radiotherapy as rather modest.

Although they considered RT effective for painful bone metastases, painful local disease, brain metastases and spinal cord compression, it seems, for instance, difficult for them, but also for second line specialist, to decide when a patient with a (threatening) spinal cord compression should be referred for palliative radiotherapy: for such patients any delay in treatment might decrease the chance of recovery but almost 30% was referred on Fridays. This indicates that most referrals and diagnoses are made in the second half of the week which suggests a delay in this process. Despite many discussions in the multidisciplinary oncology meetings, a repetition of the described study in later years (1998 to 2004) showed that the referral pattern for spinal cord compression only changed moderately.

More education seems desirable for general practitioners, but also for second line specialists more extensively about the effectiveness of radiotherapy in a variety of common palliative situations.[39-42]

Future perspectives

In this thesis we studied the use of radiotherapy in a region with only community hospitals. However, surgeons and medical oncologists from nearby academic centres (Rotterdam and Nijmegen) attend multidisciplinary oncological meetings at a regular basis. It would be interesting to investigate the referral patterns of radiotherapy in regions with an academic department, as academic radiation oncologists might be more persuading in selling the advantages of radiotherapy.

In the near future radiotherapy equipment and personnel planning purposes should of course not only be determined by the past experiences but also by applying desirable changes based upon up to date technology. Based upon the results of this thesis, more interest and knowledge in geriatric patients may lead to a better assessment of specific indications for radiotherapy. Also education in opportunities for palliative treatment might increase the awareness of possibilities to treat patients with palliative indications.

More sophisticated radiation equipment and the development in radiation methods might lead to better effectiveness and fewer complications (table 1). Developments in new techniques are a continuous process. Some tumours are better suited to a certain technique (for instance IMRT was developed for prostate cancer), but eventually more sophisticated techniques will be used for all types of cancer.

Eventually it seems extremely important for radiation oncologists to communicate closer with referring doctors about pro's and contras of radiotherapy, both short- and long-term, of course within the multidisciplinary setting.

Table 1 - New developments in radiotherapy (RT)

New developments	Breast cancer	Urological malignancies	Rectal cancer	Gynaecological malignancies	Lung cancer	Head/Neck malignancies	Primary central nervous system malignancies
Stereotactic RT					X (stage I)	X	X
Image Guided RT (IGRT)		X		X	X	X	
Conformal RT based on CT planning	X						
Partial irradiation	X						
Intensity Modulated RT (IMRT)	X	X	X	X		X	
4D Radiotherapy					X	X (vocal cords)	

Conclusions

Large variation existed in the use of radiotherapy worldwide, regarding regions, hospitals, age and co-morbid conditions. Radiotherapy is a third-line specialism, because of which radiation oncologists might work relatively isolated, even though they are essential for adequate oncological care in up to 45% of all cancer patients. Although in our studies the main trends in radiotherapy use followed the same pattern in both the western and eastern part of the region (with their distinctive referral patterns), radiotherapy consumption in the eastern part was somewhat higher for all subgroups.

Especially with the ageing of the population in the near future more knowledge is required of the best way to treat elderly people with cancer in relation to their overall condition. Prospective studies on this topic are needed, taking into account the heterogeneity of patients and being published also in non-radiotherapy journals.

It is obvious that it remains important to discuss all cancer patients early after diagnosis in multidisciplinary meetings, in which all possible treating specialists are represented.

Eventually some variations will remain because of individual differences between doctors and also between patients.

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Summary

This thesis describes the use of radiotherapy in the south of the Netherlands, a region with two large radiotherapy institutes, one covering the eastern part of the region with hospitals in the cities Eindhoven, Geldrop , Helmond, Veghel/Oss and Venlo, one covering the western part with hospitals in the cities Tilburg, Breda and 's Hertogenbosch, 10 general hospitals (as a result of merges among 20 hospitals 25 years ago) and an ageing population of 2.4 million habitants. The Eindhoven Cancer Registry and the well kept registries of the radiotherapy institutes were used as the data sources.

In **chapter 2** we described long-term trends and variations in the use of primary radiotherapy (RT) which is defined as RT given or planned within 6 months of diagnosis.

Referral rates and time trends in the RT use in the western region for cancer patients first diagnosed between 1988 and 2002 were described in **chapter 2.1**. The number of patients receiving RT within 6 months of diagnosis increased by about 3.3% annually, which was due mainly to earlier detection and the ageing of the population. The proportion of all incident cases that received primary RT remained stable at about 30%. However, only 20% of patients aged 75 years or older received RT. The proportion of patients who received primary RT increased markedly between 1988-92 and 1998-2002 for patients with prostate cancer (because of the growing number of older men and the widespread use of the PSA-test since 1994), rectal cancer (because of the shift from post- to preoperative RT since 1995) and brain tumours. The absolute number of irradiated breast cancer patients increased 30% between 1988 and 2002 because of the introduction of the biannual mass mammography screening, initially among women of 50 to 69 and since 1998 also up to age 75, and the increase in number of patients who received breast-conserving therapy. The percentage of irradiated patients with stage I endometrial cancer decreased because of participation in the Portec-trial (pelvic radiotherapy or no further treatment after total abdominal hysterectomy for patients with stage I endometrial cancer) and later because of adherence to treatment guidelines which were developed from the results of this trial.

Referral for primary RT in the western region varied according to hospital size between 1988 and 1999 (**chapter 2.2**). Specialists from medium-sized and small hospitals referred breast cancer patients significantly more often and patients with prostate cancer less often than specialists from large hospitals. Referral rates for patients with non-small cell lung and rectal cancer showed minor differences according to hospital size, referral for endometrial cancer was somewhat higher for patients from medium-sized hospitals. Time-trends in variation were shown, but differences according to hospital size only decreased over time for rectal cancer. Despite treatment guidelines and increasingly held multidisciplinary oncology meetings large variations remained in rates of referral for radiotherapy.

The purpose of **chapter 2.3** was to explore still existing variations in the use of primary radiotherapy in the region of the Eindhoven Cancer Registry.

We calculated the proportion of all 147,588 newly diagnosed cancer patients between 1988 and 2006 receiving primary radiotherapy, according to referral to the RT department in the western or eastern region, with emphasis on breast and rectal cancer.

The number of newly diagnosed patients receiving primary RT increased from 1668 in 1988 to 2971 in 2006, the proportion remained more or less stable in the western region (±30%) but increased to 35% between 2003 and 2006 in the eastern region. Only 20% of elderly patients (≥ 75 years) received primary RT, slightly more in the eastern area.

Over time, more irradiation was administered to patients with prostate and rectal cancer, less to patients with lung and bladder cancer or Hodgkin's lymphoma and recently more to patients with cervix or endometrial cancer. The proportion remained more or less unchanged for patients with most other tumour types and became slightly higher in the eastern region. For patients with breast or rectal cancer a large variation existed between individual hospitals concerning percentage irradiated patients and such patients from the eastern part of the region were significantly more likely to receive primary RT.

In **chapter 3** especially the use of secondary radiotherapy (SRT), which was defined as RT given 6 months or later after primary diagnosis or RT given after a previous course of radiation for the same tumour, was described in two population-based cohorts, which were followed until 2005.

In a cohort of 6561 patients with invasive breast cancer diagnosed between 1996-2000 with a median follow up of 66 months, 3554 patients received only primary radiotherapy (PRT), 323 only SRT and 503 both. The cumulative use of RT went from 54% during the first 6 months after diagnosis to 67% during the follow-up until 2005. The 826 patients receiving SRT underwent 1846 courses 0-105 months after diagnosis; the retreat-rate was 35%. Elderly patients received SRT significantly less often. Patients who received PRT and patients who underwent mastectomy including axillary node dissection as well as unresected patients had a higher chance to receive SRT. Despite a lower rate of mastectomy, SRT was administered more often to patients from the eastern region (**chapter 3.1**).

In a cohort of 2008 rectal cancer patients newly diagnosed between 1996-2000 46% of all patients received RT. Ten percent (203 patients) received at least once SRT, for recurrence or for metastases, either after PRT or as first RT. These patients were significantly younger and had a higher tumour stage. Five percent (96 patients) received SRT for a relapsed rectal tumour (31 after PRT on the rectal tumour, 65 as a first radiation treatment). Secondary pelvic irradiation was more often given to patients with a stage III tumour, and was significantly less often given after primary irradiation, and to patients treated in the eastern region, in which region patients received more often PRT for rectal cancer (**chapter 3.2**).

The aim of **chapter 4** was to study the influence of age and co-morbidity on receiving RT in primary treatment of cancer. This was possible because the Eindhoven Cancer Registry has collected data on co-morbid conditions since 1993.

Furthermore an overview is given of treatment possibilities of rectal cancer over time, but also of the real management of rectal cancer especially in relation to age.

In **chapter 4.1** the influence of age and co-morbidity (such as chronic obstructive pulmonary diseases, cardiovascular and cerebrovascular diseases, other malignancies (excluding basal cell carcinoma of the skin), diabetes mellitus, hypertension, connective tissue disease, rheumatoid arthritis, kidney, bowel and liver diseases, dementia, tuberculosis and other chronic infections) was described for different tumour types, all first diagnosed between 1995 and 2002. Patients with localised non-small cell lung cancer (NSCLC) aged 65 or older or with co-morbid conditions received RT alone significantly more often compared to younger patients or those without co-morbidity. This also applied for patients with non-localised NSCLC aged 65-79 years compared to younger patients. RT was administered significantly less often to elderly (≥ 65 years) with resected rectal cancer, with breast cancer after conserving surgery aged ≥ 80 years and with cT1-cT3 N0 M0 prostate cancer aged ≥ 80 years than to younger patients. Breast cancer patients undergoing breast-conserving surgery received significantly less often RT in the presence of co-morbidity. Older patients with aggressive non-Hodgkin lymphoma received RT as only treatment significantly more often compared to younger patients. For most tumour types age appeared to be a stronger predicting factor for receiving radiotherapy than co-morbidity. Under-treatment was found for patients with breast cancer or rectal cancer.

To give insight in the influence of age on the treatment of rectal cancer patients we reviewed the literature on population-based studies describing radiotherapy or radiotherapy in combination with chemotherapy for resectable rectal cancer. All studies showed that increasing age was associated with less (neo)adjuvant treatment. Also a literature search on representative randomised trials on patients with resectable rectal cancer, comparing only surgery, post- and preoperative radiotherapy with or without chemotherapy, was done. This overview showed that preoperative radiotherapy improves local control in relation to no or postoperative radiotherapy. Adding chemotherapy did not significantly improve survival. No relations were seen between age and complications. To avoid local recurrence, the best possible treatment, being preoperative RT, should be given to all patients with resectable rectal cancer, irrespective of age, except to patients who are unable to fulfil the combination treatment because of patient's condition (**chapter 4.2**).

The knowledge of palliative RT was discussed in **chapter 5**. In **chapter 5.1** the results are described of a questionnaire, sent to all general practitioners in the region of the Comprehensive Cancer Centre South, to obtain insight into the knowledge of palliative RT among general practitioners. Four hundred and ninety-eight of 1100 questionnaires were analysed. Forty-six percent of the respondents had referred palliative-care patients for RT in the last 2 years. The knowledge about palliative RT for bone metastases and spinal cord compression was good, for other palliative indications it was moderate to poor.

General practitioners also considered their own knowledge poor, only 10% received RT education in the past. Factors influencing the actual referral for palliative RT were mainly patient-related.

Between 1987 and 1997 the speed of referral of patients with spinal cord compression was analysed based on a tumour and treatment related registry of the RT institute in the western region. All 443 patients were seen and treated on the day of referral. Significantly more referrals took place on Friday, 30%, compared to 12% on Monday, 17% on Tuesday, 15% on Wednesday, 20% on Thursday, 5% on Saturday and 1% on Sunday ($p<0.002$). This difference was the same for patients who were formerly treated in the institute or not. These data were discussed with referring physicians and have been presented at a scientific meeting of the comprehensive cancer centre to encourage speed of diagnosis and referral (**chapter 5.2**).

In **chapter 6** the results from this thesis and some future perspectives were discussed. To obtain the optimal treatment for an individual patient it remains important to discuss the case early after the diagnosis in multidisciplinary meetings, in which all possible treating specialists are represented. Furthermore, radiation oncologists, as third-line, relatively isolated working specialists, should also publish in journals which are relevant for referral specialists. The overall conclusion is that some variation in radiotherapy use will remain because of individual differences between doctors and between patients.

Samenvatting

Variatie in het gebruik van radiotherapie voor kankerpatiënten.

Population-based studies in het zuiden van Nederland

Dit proefschrift beschrijft het gebruik van radiotherapie voor patiënten met kanker in Zuid-Nederland, een regio met een verouderende populatie van 2.4 miljoen en twee grote radiotherapie instituten. De radiotherapie afdeling van het Catharina Ziekenhuis te Eindhoven, in 1973 voortgekomen uit het in 1954 opgerichte Radiotherapeutisch Instituut, verzorgt het oostelijke deel van de regio, met ziekenhuizen in Eindhoven, Geldrop, Helmond, Veghel/Oss en Venlo. Het Dokter Bernard Verbeeten Instituut in Tilburg, opgericht in 1952 als Radio-Therapeutisch Instituut Tilburg, is een zelfstandig instituut en verzorgt het westelijke deel van de regio, met ziekenhuizen in Tilburg, Den Bosch en Breda. In totaal bevinden zich in de regio nog 10 algemene ziekenhuizen, die ontstaan zijn door fusies van 20 ziekenhuizen in de laatste 25 jaar. De Eindhovense kankerregistratie en de goed bijgehouden registraties van de radiotherapie instituten werden gebruikt als bron voor alle studies in dit proefschrift. Sinds 1986 worden alle kankerpatiënten in bovengenoemde regio's geregistreerd door de Eindhovense kankerregistratie, voortgekomen uit de in 1955 opgerichte regionale kankerregistratie van het Radiotherapeutisch Instituut in Eindhoven. De kankerregistratie is een onderdeel van het Integraal Kankercentrum Zuid, een kennis- en kwaliteitscentrum op het gebied van de oncologie en de palliatieve zorg, opgericht eind 1982.

De radiotherapeut-oncologen wonen, als consulenten, vele oncologiebesprekingen bij in de verschillende ziekenhuizen in de regio. Hier worden (bijna) alle nieuwe patiënten met kanker en de patiënten met moeilijk te behandelen recidieven of metastasen besproken.

De radiotherapeut-oncologen hebben ook zitting in de verschillende tumorwerkgroepen in de regio. In deze groepen wordt (regionaal en landelijk) beleid en deelname aan studies besproken. Het Dokter Bernard Verbeeten Instituut neemt van oudsher op grote schaal deel aan EORTC en andere klinische studies, terwijl de afdeling Radiotherapie van het Catharina Ziekenhuis een traditie kent van (deelname aan) observationeel onderzoek sinds 25 jaar in verband ook van het SOOZ (Samenwerkingsorgaan Oncologie Ziekenhuizen).

De belangrijkste vraagstellingen die in dit proefschrift aan bod komen zijn de volgende:

- Wat waren de tumorspecifieke trends in het gebruik van primaire radiotherapie?
- Welke variatie bestond er in de verwijzingspatronen, kijkend naar diagnostiserend ziekenhuis, leeftijd en bijkomende ziekten?
- Welk percentage patiënten met borst- of rectumkanker ontving secundaire radiotherapie?
- Bij een vermoede onderconsumptie, hoe is de kennis bij andere specialisten en huisartsen betreffende palliatieve radiotherapie?

In **hoofdstuk 2** werden langetermijntrends en variaties in het gebruik van primaire radiotherapie (RT) beschreven. Primaire RT werd gedefinieerd als RT gepland of gegeven binnen 6 maanden na de diagnose.

In **hoofdstuk 2.1** werden trends in de tijd en verwijzingspatronen besproken voor kankerpatiënten met een diagnose tussen 1988 en 2002 in het deel van de regio dat bestreken wordt door het Dokter Bernard Verbeeten Instituut. Het aantal patiënten dat bestraald werd binnen 6 maanden na de diagnose kanker steeg jaarlijks met 3,3%.

Dit was voornamelijk toe te schrijven aan eerdere ontdekking van de tumor en aan het ouder worden van de populatie. Het percentage bestraalde patiënten bleef stabiel en lag rond de 30%, maar van de patiënten ouder dan 75 jaar werd maar 20% bestraald.

Het percentage patiënten dat primaire RT ontving, steeg opvallend tussen de periode 1988-1992 en 1998-2002 voor patiënten met de volgende tumorsoorten:

- prostaatkanker (door het toenemende aantal oudere mannen in de populatie en als gevolg van het wijdverbreide gebruik van de PSA-test sinds 1994),
- endeldarmkanker (door de verschuiving van post- naar preoperatieve RT sinds 1995),
- hersentumoren (door bestraling van patiënten ouder dan 55 jaar met een hooggradig astrocytoom).

Het absolute aantal patiënten met borstkanker dat bestraald werd, steeg met 30% tussen 1988 en 2002 door de introductie van de tweejaarlijkse screening - in eerste instantie voor vrouwen tussen 50 en 69 jaar en sinds 1998 ook tot 75 jaar - waarbij tussen 1990 en 1995 jaarlijks 10% meer vrouwen een borstsparende behandeling ondergingen.

Het percentage bestraalde patiënten met een stadium I endometriumcarcinoom daalde in eerste instantie door de aanzienlijke participatie in de Portec-trial (bestraling op het bekken of geen verdere therapie na een totale abdominale hysterectomie voor patiënten met een stadium I endometriumcarcinoom). Een verdere daling werd gezien bij jongere vrouwen naar aanleiding van de resultaten van de Portec-trial; hierbij komen alleen patiënten ouder dan 60 jaar met een endometriumcarcinoom stadium Ia en Ib graad 3 of een stadium Ic en patiënten jonger dan 60 jaar met een stadium Ic graad 3 in aanmerking voor postoperatieve radiotherapie.

In de westelijke regio varieerde de verwijzing naar primaire radiotherapie tussen 1988 en 1999 tussen de verschillende ziekenhuizen meer dan een factor anderhalf; dit bleek met name afhankelijk van de grootte van de ziekenhuizen (**hoofdstuk 2.2**). Specialisten uit middelgrote en kleine ziekenhuizen verwezen significant meer patiënten met borstkanker en significant minder patiënten met prostaatkanker voor primaire RT dan specialisten uit de grote ziekenhuizen. De verwijzingspatronen voor patiënten met niet-kleincellig longcarcinoom en rectumcarcinoom verschilden weinig wat betreft de ziekenhuisomvang. Patiënten met endometriumcarcinoom werden iets vaker verwezen door specialisten uit middelgrote ziekenhuizen.

Trends in de tijd in het gebruik van primaire RT lieten alleen kleinere variaties zien bij rectumcarcinoom. Dus ondanks behandelingsrichtlijnen en het toenemende aantal multidisciplinaire oncologie bijeenkomsten bleven bovengenoemde variaties bestaan in de verwijzingspatronen naar radiotherapie.

In **hoofdstuk 2.3** werd het onderzoek naar trends in het primaire radiotherapie gebruik voortgezet tot en met 2006. Bovendien werden in deze studie alle patiënten uit zowel de westelijke regio (het Dokter Bernard Verbeeten Instituut), als de oostelijke regio (de afdeling radiotherapie van het Catharina Ziekenhuis) geïncludeerd. Dit gaf ons de mogelijkheid om verschillen tussen de beide regio's te onderzoeken, uitgebreider voor borst- en rectumkanker.

Het totaal aantal primair bestraalde patiënten per jaar bleef stijgen, maar het percentage bestraalde patiënten bleef fluctueren tussen 30 en 32%, waarbij het in de westelijke regio 30% bleef, maar in de oostelijke regio steeg naar 35% in de periode 2003-2006. In beide regio's werden, bij gelijke indicaties, patiënten ouder dan 75 jaar minder vaak bestraald dan jongere patiënten, waarbij ook hier het verschil tussen de regio west (rond 18%) en oost (23% in 2003-2006) opvallend was.

Het percentage patiënten met rectum- en prostaatkanker dat bestraald werd, steeg verder in de periode 2003-2006. Het percentage bestraalde patiënten met cervix- of endometriumcarcinoom steeg in de laatste periode, na een eerdere daling; dit is waarschijnlijk toe te schrijven aan het verschijnen van nieuwe richtlijnen voor beide tumorsoorten in 2004. Het percentage bestraalde patiënten met long- en blaaskanker en met en Hodgkin-lymfoom daalde.

Tot 1995 fluctueerde het percentage bestraalde patiënten met borstkanker tussen de 57 en 62% in zowel de regio west als oost van het IKZ. Hierna vond een divergentie plaats, waarbij in de westelijke regio een daling werd gezien tot 54% en in de oostelijke regio een stijging tot 69%. Overeenkomstig deze trends in radiotherapie gebruik vonden we in de regio west een lager percentage patiënten dat borstsparende chirurgie, en een hoger percentage dat een amputatie onderging. In 2006 leken de percentages van beide chirurgische ingrepen te convergeren.

Vanaf 1995 werd, eerst in de oostlijke regio, preoperatieve bestraling voor het rectumcarcinoom geïntroduceerd: een korte serie voor een operabel, en een lange serie voor een plaatselijk voortgeschreden tumor. In 2004 werd 50% van alle patiënten met endeldarmkanker preoperatief bestraald. Patiënten met rectumcarcinoom uit de regio oost werden significant vaker bestraald.

Voor beide bovengenoemde tumorsoorten bestond een grote variatie tussen de 10 ziekenhuizen in de regio wat betreft het percentage bestraalde patiënten.

In **hoofdstuk 3** werd vooral ingegaan op het gebruik van secundaire RT in twee cohorten met patiënten uit beide regio's, die werden gevolgd tot 2005. Secundaire RT werd gedefinieerd als RT gegeven zes maanden of later na de primaire diagnose, of RT gegeven na een eerdere bestralingsbehandeling voor dezelfde tumor; deze wordt over het algemeen gegeven op recidieven en/of metastasen.

Het eerste cohort (**hoofdstuk 3.1**) bestond uit 6561 patiënten met een invasief mammacarcinoom, gediagnostiseerd tussen 1996 en 2000 en met een mediane follow-up van 66 maanden. 3554 patiënten (54%) ontvingen alleen primaire RT, 323 (5%) alleen secundaire RT en 503 patiënten (8%) zowel primaire als secundaire RT.

Het cumulatieve gebruik van RT steeg van 54% gedurende de eerste 6 maanden naar 67% gedurende de follow-up tot 2005. De 826 patiënten die secundaire RT ontvingen, kregen in totaal 1846 RT series 0 tot 105 maanden na de diagnose; het percentage herbehandelingen was 35%.

Oudere patiënten werden beduidend minder vaak secundair bestraald. Patiënten die primaire RT ontvingen, patiënten die een mastectomie inclusief een okselkliertoilet ondergingen en patiënten die niet geopereerd werden, hadden een significant hogere kans om secundair bestraald te worden. Ondanks het lagere percentage patiënten dat een mastectomie onderging in de oostelijke regio, werden patiënten uit deze regio vaker secundair bestraald (14%) dan patiënten uit de westelijke regio (11.5%). Dit verschil was het grootst in de jongere leeftijdsgroepen.

In het tweede cohort (**hoofdstuk 3.2**) werd 46% van alle 2008 patiënten met een rectumcarcinoom, gediagnostiseerd tussen 1996 en 2000, bestraald. Tien procent (203 patiënten) ontving ten minste een keer secundaire RT, van wie 94 patiënten na primaire RT (11% van primair bestraalden). De patiënten die secundair bestraald werden, waren significant jonger en hadden een minder gunstige tumor stadiëring.

Binnen een periode van drie jaar na de incidentiedatum werd vier procent (79 patiënten) secundair bestraald op een recidief van het rectumcarcinoom. Tweeëntwintig van deze patiënten waren al eerder bestraald op de rectum tumor, voor 57 patiënten was het de eerste bestralingsbehandeling. Binnen 5 jaar was dit vijf procent (96 patiënten, van wie 31 patiënten eerder waren bestraald en 65 niet). Secundaire bestraling op het rectum werd vaker gegeven aan patiënten met een stadium III tumor dan een stadium II en minder vaak aan patiënten die primair op het rectum waren bestraald. Ook patiënten uit de oostelijke regio werden minder vaak secundair op het rectum bestraald. Daar werden patiënten vaker primair bestraald op het rectumcarcinoom.

Het doel van **hoofdstuk 4** was om de invloed van leeftijd en bijkomende ziekten bij diagnose op het gebruik van primaire RT te bestuderen. Dit was mogelijk omdat de Eindhovense Kankerregistratie sinds 1993 op verzoek van de klinici, onafhankelijk van de radiotherapie, gegevens heeft verzameld betreffende ernstige bijkomende ziekten.

Bovendien werd onderzocht in de literatuur hoe oudere patiënten met een rectumcarcinoom behandeld werden, waaraan voorafgaand een overzicht werd gegeven van de behandelingsmogelijkheden van het rectumcarcinoom in de loop der tijd.

Hoofdstuk 4.1 gaat over de invloed van leeftijd en bijkomende ziekten zoals chronisch obstructieve longziekten, cardiovasculaire en cerebrovasculaire ziekten, andere maligniteiten (exclusief basaalcelcarcinoom van de huid) diabetes mellitus, hypertensie, bindweefselziekten, rheumatoide artritis, nier-, darm- en leverziekten, dementie, tuberculosis en andere chronische

infecties. Het omvat patiënten uit de regio's west en oost met longkanker, rectumcarcinoom, borstkanker, prostaatkanker of non-Hodgkin-lymfoom, gediagnostiseerd tussen 1995 en 2002.

Patiënten met een gelokaliseerd niet-kleincellig longcarcinoom ouder dan 65 jaar of met bijkomende ziekten kregen vaker RT als enige behandeling ten opzichte van jongere patiënten of patiënten zonder bijkomende ziekten. Ditzelfde gold ook voor patiënten met een niet-gelokaliseerd carcinoom tussen de 65 en 79 jaar.

Significant minder vaak bestraald werden oudere patiënten met een geopereerd rectumcarcinoom, borstkanker patiënten van 80 jaar en ouder na borstsparende chirurgie en prostaatkanker patiënten van 80 jaar en ouder met een cT1-cT3 N0 M0 tumor. Patiënten met borstkanker en bijkomende ziekten werden na een borstsparende behandeling significant minder vaak bestraald.

Bij oudere patiënten met een agressief non-Hodgkin-lymfoom was bestraling vaker de enige behandeling dan bij jongere patiënten (tabel 1).

Tabel 1 - De invloed van leeftijd en co-morbiditeit op radiotherapie gebruik bij verschillende kanker soorten

Tumor soort	Stadium	Soort behandeling	Radiotherapie bij ouderen (≥65 of ≥80 jaar of ≥70 jaar) ten opzichte van jongeren	Radiotherapie bij patiënten met co-morbiditeit ten opzichte van patiënten zonder co-morbiditeit
Longkanker, niet-kleincellig	I en II	Alleen radiotherapie	Meer (≥65 jaar)	Meer
Longkanker, niet-kleincellig	III	Alleen radiotherapie	Meer (≥65 jaar)	Niet verschillend
Longkanker, kleincellig	Limited disease	Alleen radiotherapie	Meer (≥65 jaar)	Niet verschillend
Rectumkanker	I-III	Radiotherapie voor/na chirurgie	Minder (≥65 jaar)	Niet verschillend
Borstkanker		Radiotherapie na borstsparende chirurgie	Minder (≥80 jaar)	Minder
Prostaatkanker	CT1-cT3 N0 M0	Alleen radiotherapie	Minder (≥80 jaar)	Niet verschillend
Non-Hodgkin-lymfoom	Agressief	Alleen radiotherapie	Meer (≥70 jaar)	Meer

Voor de meeste tumorgroepen bleek leeftijd een sterkere voorspellende factor voor primaire radiotherapie dan de genoemde bijkomende ziekten. Vooral oudere patiënten met borstkanker of rectumcarcinoom werden veel minder vaak bestraald dan jongere patiënten, iets dat ook in de literatuur beschreven wordt.

Om inzicht te krijgen in de invloed van leeftijd op de behandeling van rectumcarcinoom, bestudeerden we de literatuur betreffende 'population-based' studies van het gebruik van RT of van RT in combinatie met chemotherapie voor het operabel rectumcarcinoom (**hoofdstuk 4.2**). Uit alle studies bleek dat hogere leeftijd geassocieerd was met minder (neo)adjuvante behandeling.

Bovendien bestudeerden we grondig de literatuur betreffende representatieve gerandomiseerde studies die chirurgie als enige behandeling, postoperatieve en preoperatieve RT (met of zonder chemotherapie) vergeleken. Preoperatieve RT bleek de lokale controle te verbeteren ten opzichte van geen of postoperatieve RT.

Toevoeging van chemotherapie gaf geen significante verbetering van de overleving. Er werd geen relatie gevonden tussen leeftijd en het optreden van complicaties na RT.

Om lokaal recidief te vermijden, moet evenwel de best mogelijke behandeling gegeven worden aan patiënten met een operabel rectumcarcinoom. Alle patiënten zouden dus preoperatief bestraald moeten worden, onafhankelijk van de leeftijd, behalve patiënten die hiertoe niet in staat zijn door hun (slechte) conditie. Om echter het risico van een dubbele belasting (radiotherapie en meteen daarna chirurgie) bij ouderen te voorkomen, zou uitgestelde chirurgie na voorbestraling een mogelijkheid zijn, iets dat nu in studieverband onderzocht wordt.

In **hoofdstuk 5** werden aspecten van palliatieve RT besproken. In **hoofdstuk 5.1** staan de resultaten van een in samenwerking met de afdeling palliatieve zorg ondernomen enquête onder alle huisartsen in de regio van het Integraal Kankercentrum Zuid, met als doel inzicht te verkrijgen in de kennis van palliatieve RT. Vierhonderdnegenentachtig van de 1100 verstuurde enquêtes werden geanalyseerd. Van de respondenten zei 47% betrokken te zijn geweest bij verwijzing van patiënten voor palliatieve RT in de afgelopen 2 jaar. De behandeling middels RT van pijnklachten bij botmetastasen en dreigende dwarslaesie was ruimschoots bekend, in tegenstelling tot andere indicaties zoals hersenmetastasen, luchtwegobstructies, hematurie of hemoptisis. Kennis over de verdere (on)mogelijkheden van RT en de bijwerkingen ervan werden door 80% van de huisartsen zelf als onvoldoende tot matig geschat. Bij de besluitvorming tot verwijzing speelden, volgens de huisartsen, vooral de wens van de patiënt en de leeftijd een belangrijke rol, iets dat mede een gevolg kan zijn van een ondervertegenwoordiging van scholing in (palliatieve) RT in de basisopleiding en daarna, zoals men aangaf. Ook in Canada, de Verenigde Staten en Japan geven huisartsen en specialisten aan dat hun kennis betreffende palliatieve radiotherapie niet optimaal is, iets dat voor een deel te wijten is aan onvoldoende scholing. Dit kan tot gevolg hebben dat RT onthouden wordt aan patiënten die er veel baat bij kunnen hebben.

Tussen 1987 en 1997 werd de snelheid van verwijzing naar RT onderzocht bij patiënten met een (dreigende) dwarslaesie door tumoringroei in het ruggenmerg, met behulp van de tumor- en therapieregistratie in de database van het RT instituut in het westelijke deel van de regio. Alle 443 patiënten met een (dreigende) dwarslaesie werden gezien en behandeld op de dag van verwijzing.

Er vonden significant meer verwijzingen plaats op vrijdag, namelijk 30%, vergeleken met 12% op maandag, 17% op dinsdag, 15% op woensdag, 20% op donderdag, 5% op zaterdag en 1% op zondag (P=<0.002). Het maakte geen verschil of patiënten al in het instituut bekend waren of niet.

Deze bevindingen werden bediscussieerd met de verwijzende specialisten op een wetenschappelijke bijeenkomst in de regio om hen aan te sporen tot spoed bij diagnose en verwijzing, maar anno 2008 lijkt het patroon vrijwel onveranderd (**hoofdstuk 5.2**).

Hoofdstuk 6 bevat een algemene bespreking van de resultaten. 'Population-based' studies geven in beginsel een reëel inzicht in het gebruik van radiotherapie en variatie daarin in plaats en tijd: uit de trendstudies bleek dat het percentage patiënten dat radiotherapie in het kader van de primaire behandeling ontving, stabiel bleef tussen 1988 en 2006, maar dat er verschillen waren tussen de westelijke en oostelijke regio van het Integraal Kankercentrum Zuid; uit de cohort studies, waarmee tevens het gebruik van radiotherapie in het kader van recidief of metastase bestudeerd kan worden (secundaire radiotherapie), bleek dit verschil ook. Tevens bleek dat ouderen minder vaak bestraald werden en dat de kennis betreffende toepassing van palliatieve radiotherapie verbeterd zou kunnen worden. Ook worden in hoofdstuk 6 enkele toekomstige ontwikkelingen besproken.

We kunnen concluderen dat het van groot belang blijft dat patiënten zo vroeg mogelijk na de diagnose besproken worden in multidisciplinaire oncologie besprekingen. Het ligt voor de hand dat radiotherapeut-oncologen, als 3^{e}-lijns, relatief geïsoleerd werkende specialisten, vooral ook publiceren in tijdschriften die relevant zijn voor verwijzende 2^{e}-lijns specialisten. Uiteindelijk zal er enige variatie blijven bestaan door individuele verschillen tussen artsen en tussen patiënten.

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Curriculum vitae

Geboren: 17-01-1957 te Vleuten-De Meern.

1975:	diploma gymnasium B aan het Bonifatius College te Utrecht.
1975-1982:	studie Geneeskunde aan de Rijksuniversiteit te Utrecht.
1983-2007:	verbonden aan het Dr. Bernard Verbeeten Instituut voor radiotherapeutische oncologie en nucleaire geneeskunde te Tilburg als 'registratie-arts', een functie die in de loop der jaren is uitgebouwd van het registreren van patiënten- en therapiegegevens in de eigen database van het instituut tot het beheren en bewerken van deze database en het doen analyses met gegevens uit de database.
2000-2003:	postdoctorale opleiding epidemiologie aan de Vrije Universiteit te Amsterdam. Tijdens de stage van deze opleiding werd als stage-onderwerp bestudering van radiotherapie gebruik en variaties hierin gekozen. Deze studies hebben de kiem gelegd voor dit proefschrift.

Getrouwd sinds 1984 met Louis Mulders; 2 zonen: Bram en Rik.

List of publications

Articles in this thesis:

1. Vulto A, Louwman M, Rodrigus P, Coebergh JW. Referral rates and trends in radiotherapy as part of primary treatment of cancer in South Netherlands, 1988-2002. *Radiother Oncol* 2006;78:131-137.

2. Vulto JC, Louwman WJ, Poortmans PM, Coebergh JW. Hospital variation in referral for primary radiotherapy in South Netherlands, 1988-1999. *Eur J Cancer* 2005;41:2722-2727.

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4. Vulto JC, Louwman WJ, Poortmans PM, Lybeert LM, Rutten HJ, Coebergh JW. A population-based study of radiotherapy in a cohort of patients with breast cancer diagnosed between 1996 and 2000. *Eur J Cancer* 2007;43:1976-1982.

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