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Changes in the use of chemoradiotherapy for non-small cell lung cancer after guideline implementation in Finland between 2016 and 2020

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ABSTRACT

Background: Following treatment with chemoradiotherapy (CRT), approximately 30 % of patients with stage III unresectable non-small cell lung cancer (NSCLC) can achieve long-term remission with the possibility of a cure. [1,2,3]. CRT was deemed to be underutilized in Finland compared with the lung cancer incidence. Herein, we examined the potential increase in CRT use following the introduction of national guidelines to improve and standardize NSCLC treatment nationally.

Materials and methods: We compared the use of CRT before and after the implementation of updated CRT guidelines in 2016 and 2020. Data was gathered on all patients treated with CRT from every radiotherapy unit, in Finland, for a total of 13 radiotherapy units.

Results: Overall, 53 and 77 patients with NSCLC were treated with CRT in 2016 and 2020, respectively; thus, CRT use increased significantly by 45 %. There was only a slight overall increase in the incidence of lung cancer, with 2734 patients reported in 2016 and 2801 in 2020, according to the Finnish Cancer Registry report from 2020. Overall (OS) and progression-free survival (PFS) were analyzed over 2 years. The median PFS was 10 and 15 months in patients treated in 2016 and 2020, respectively. The median OS was not reached in either group. There were no statistically significant differences between the groups.

Conclusion: Implementation of the national guideline increased CRT use and altered clinical practice across the country, without compromising treatment efficacy or survival. CRT was provided more uniformly after the implementation of national guidelines.

Introduction

The overall incidence of lung cancer in Finland is 60.3 in males and 33.7 in females per 100,000, with an estimated 2801 new cases reported annually, according to the 2020 Finnish Cancer Registry report [1]. Non-small cell lung cancer (NSCLC) reportedly accounts for 85 % of the

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total lung cancer cases, and approximately 20 % of patients with NSCLC are diagnosed as stage III [2]. Disease stage at diagnosis can substantially affect survival. According to the 2013–2019 report of the Surveillance, Epidemiology, and End Results (SEER) database statistics, the 5-year relative survival was 62.8 % in patients with localized stage I-II disease, 34.8 % in those diagnosed with regional stage III, and 8.2 % in patients diagnosed with metastatic stage IV NSCLC [3].

Chemoradiotherapy (CRT) emerged as a treatment option for inoperable stage III NSCLC in the 1990s. In studies on patients with stage III NSCLC receiving CRT, the median overall survival (OS) ranged between 20 and 30 months, and the 5-year OS was ~20 % [4–6], indicating the substantial benefits of CRT over systemic therapy alone. In the PACIFIC study, the addition of durvalumab further improved the effects elicited by conventional CRT. The 5-year OS in the durvalumab arm was 42.9 % vs. 33.1 % in the placebo arm [7].

CRT can be demanding for the patient, who typically experiences severe adverse events (AEs). Meticulous patient selection is crucial, considering the disease extent, baseline performance status, lung functions, and concurrent medications. Smoking cessation should be encouraged in active smokers to improve treatment outcomes and reduce side effects [8]. The development of radiation techniques, in conjunction with good practice and supportive care, has enabled an increasing number of patients to undergo planned treatments. In Europe, CRT-treated programmed death-ligand 1 (PD-L1)-positive patients are eligible for adjuvant 1-year immunotherapy with durvalumab if no progression is detected at CRT completion.

The 2017 Finnish National Guidelines recommend the administration of concurrent CRT at 60–66 Gy in 2 Gy fractions with platinum-based chemotherapy [9]. Likewise, the current National Comprehensive Cancer Network (NCCN) guidelines (version 5.2023) recommend CRT at 60–70 Gy to treat inoperable stage III NSCLC along with platinum-based chemotherapy. Additionally, the NCCN guidelines suggest the use of neoadjuvant and sequential administration of chemotherapy [10].

In Finland, CRT was deemed to be underutilized, and treatment implementation appears to be heterogeneous. The Finnish National Guidelines recommend the use of CRT to treat inoperable stage III NSCLC, although the precise dose has not been suggested. Therefore, a more specific treatment guideline was urgently warranted, along with its implementation. Accordingly, based on the American Society of Radiation Oncology (ASTRO) and NCCN guidelines, a specific guideline for CRT was established in 2020 in a national consensus meeting [10–12]. The newly established Finnish Guideline on CRT provides specific instructions on pre-treatment workup, treatment planning, chemotherapy dosing, and patient follow-up during the treatment. The recommended radiotherapy fractionation is 60–66 Gy in 2 Gy fractions. Platinum-based chemotherapy (cisplatin-etoposide (Etoposide), carboplatin-paclitaxel, or cisplatin-vinorelbine) is recommended as a chemosensitizer. The recommended fractionation and chemotherapy agents are well-established in prior clinical studies [4–6]. For implementation purposes, a nationwide meeting was held, and consensus on shared guidelines was reached.

The purpose of the current study was to enhance, improve, and standardize NSCLC treatment practice at a national level by guideline intervention. To this end, we collected information on all CRT-treated patients nationwide during a 1-year period before and after the guideline implementation.

Methods

Study design & setting

This nationwide retrospective study was performed by independent investigators across all radiotherapy units in Finland and coordinated by the CRT Working Group at Vaasa Central Hospital and Tampere University Hospital on behalf of the Finnish Lung Cancer Group (FLCG).

During the first phase, we collected data on patients who underwent CRT between January 1, 2016, and December 31, 2016, based on treatment start date. In the second phase, a new guideline for CRT in stage III NSCLC was developed during an FLCG meeting and distributed to all radiotherapy units. Following guideline implementation in February 2020, we collected data on patients treated with CRT from April 4, 2020, to March 31, 2021. Data collection for phase one concluded on March 18, 2021, and for phase two on August 5, 2022.

Participants

Eligible patients had histologically confirmed, stage III, locally advanced, unresectable NSCLC and received curative-intent concurrent or sequential CRT. An additional inclusion criterion was that the last chemotherapy dose had been administered within three months prior to starting radiotherapy.

Data sources

Data were obtained from all 13 Finnish radiotherapy units, including university hospitals, central hospitals, and one private hospital. The patients were identified from radiotherapy unit registries (ARIA) with procedure code WF002 (National Institute for Health and Welfare) and associated ICD-10 code of C34. Standardized data collection forms were distributed to all participating units to ensure consistency. To achieve uniform classification and reporting where applicable, commonly used clinical classification systems (e.g., TNM staging, ECOG performance status, RECIST for tumor response, and CTCAE for adverse event grading) were applied according to each center's standard practice. Data were collected retrospectively with authorized permission from Findata. The study protocol was approved by The Ethics Committee for Human Sciences at the University of Turku, Health care division, approval number 11/2020. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Measurements

The primary outcome was the number of patients receiving CRT before and after guideline implementation. Secondary outcomes included progression-free survival (PFS), overall survival (OS), adverse events including hospitalization, treatment discontinuation, and death within 30 days of completing radiotherapy. Detailed patient characteristics and precise treatment delivery parameters were also recorded.

Statistical methods

As this was a retrospective study, no formal sample size calculation was performed; all eligible patients were included to maximize statistical power. Data from the 2016 and 2020 treatment periods were compared using SPSS Statistics version 29.0.0.0 (IBM Corp., Armonk, NY, USA) in the Findata Kapseli platform. Descriptive statistics were used to summarize baseline characteristics. Time-to-event outcomes were analyzed using the Kaplan–Meier method and compared with the log-rank test. Two-sided p-values <0.05 were considered statistically significant, and 95 % confidence intervals (CIs) were reported.

Results

The 2016 data

In 2016, 53 patients with NSCLC underwent CRT. The median patient age was 64 years, and 35 (66 %) patients were male. The Eastern

Table 1
Baseline patient characteristics, 2016 vs. 2020.

Year	2016	2020
Age median - yr	64	69
Male - n (%)	35 (66)	53 (68.8)
Female - n (%)	18 (34)	24 (31.2)
ECOG		
ECOG 0 - n (%)	11 (20.8)	25 (32.5)
ECOG 1 - n (%)	27 (50.9)	44 (57.1)
ECOG 2 - n (%)	12 (22.6)	4 (5.2)
ECOG 3 - n (%)	3 (5.7)	0 (0)
Comorbidity		
COPD - n (%)	19 (35.8)	21 (27.3)
Asthma - n (%)	21 (39.6)	9 (11.7)
MCC - n (%)	8 (15.1)	13 (16.9)
Hypertension - n (%)	26 (49.1)	43 (55.8)
DM - n (%)	20 (37.7)	19 (24.7)
Smoking median pack years	40	40
Stage		
Stage IIIA - n (%)	31 (58.5)	20 (26.0)
Stage IIIB - n (%)	16 (30.2)	29 (37.7)
Stage IIIC - n (%)	1 (1.9)	19 (24.7)
Stage IB - n (%)	3 (5.7)	1 (1.3)
Stage IIB - n (%)	1 (1.9)	4 (5.2)
Stage IV - n (%)	1 (1.9)	2 (2.6)
Tumor histology		
Squamous ca - n (%)	19 (35.8)	32 (41.6)
Adeno ca - n (%)	23 (43.4)	40 (51.9)
Other histology - n (%)	10 (18.9)	5 (6.5)
PD-L1 testing - n (%)	35 (43.4)	67 (87.0)
Positive PD-L1 - n (%)	6 (11.3)	49 (63.6)
EGFR testing - n (%)	35 (66)	50 (64.9)
Positive EGFR - n (%)	8 (15.1)	Not reported
ALK testing - n (%)	33 (62.3)	54 (70.1)
Positive ALK - n (%)	6 (11.3)	2 (2.6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; COPD, Chronic obstructive pulmonary disease; MCC, Coronary artery disease; DM, Diabetes mellitus, PD-L1, Programmed death-ligand 1; EGFR, Epidermal growth factor receptor; ALK, Anaplastic lymphoma kinase.

Cooperative Oncology Group performance status (ECOG-PS) was 0–1 in 38 (71.7 %) patients. Nineteen patients (35.8 %) had a squamous histologic type NSCLC. Most patients had either stage IIIA (58.5 %) or stage IIIB (30.2 %) disease. The PD-L1 status was examined in 35 patients (43.4 %), and 6 (11.3 %) were identified as PD-L1-positive. Baseline characteristics and treatments are presented in Tables 1 and 2.

After a 2-year follow-up, the median progression-free survival (PFS) was 10 months (95 % CI 8.0–12.0), and the median OS was not reached. (Fig. 1). Furthermore, 18 (34.0 %) patients had no disease progression, and 35 (66.0 %) were alive at the 2-year follow-up. The best objective responses during the imaging follow-ups were complete response (CR) in 17.5 %, partial response (PR) in 55 %, stable disease (SD) in 5 %, and progressive disease (PD) in 22.5 % of the patients.

The ECOG-PS was downgraded in 18 (33.9 %) patients during CRT. Seventeen (32.1 %) patients experienced nausea; one had grade 3 esophagitis; and two suffered a coronary event. Nineteen (35.8 %) patients needed to be hospitalized during treatment. Grade 3–4 hematological toxicity, including grade III/IV leucopenia ($n = 6$, 11.3 %) and grade III-IV thrombocytopenia ($n = 3$, 5.7 %), were also documented. All patients visited a nurse regularly, and 19 (35.8 %) visited a nutritional therapist during CRT. Table 2 presents the adverse events experienced by the patients.

The 2020 data

In 2020, 77 patients with NSCLC underwent CRT. Patient data from one radiotherapy unit was lost due to a computer failure in the radiotherapy information system; therefore, the actual number of CRT-treated patients could have been higher in 2020. The median patient age was 69 years, and 53 (68.8 %) patients were male. The ECOG-PS was 0–1 in 69 (89.6 %) patients. Thirty-two (41.6 %) had squamous histologic type NSCLC. Most patients had either stage IIIA (26.0 %), stage IIIB (37.7 %), or stage IIIC (24.7 %) disease. The PD-L1 status was examined in 67 (87.0 %), and 49 (63.6 %) were identified as PD-L1-positive. Baseline characteristics and given treatments are presented in Tables 1 and 2.

After a 2-year follow-up, the median PFS was 15 months (95 % CI 6.3–23.7), and the median OS was not reached. (Fig. 1). Thirty-three (43.0 %) patients had no disease progression, and 49 (63.6 %) were alive at the 2-year follow-up. The best response rates were as follows: CR, 19 %; PR, 55.2 %; SD, 6.9 %; and PD, 19 %.

The ECOG-PS status was downgraded in 26 (33.8 %) patients during CRT. Twenty-six (33.8 %) patients experienced nausea; two had grade 3 esophagitis; and two suffered from a coronary event. Twenty-five (32.5 %) patients needed to be hospitalized during treatment. One patient died during CRT owing to septic infection and acute kidney injury related to chemotherapy. Grade III-IV leucopenia occurred in 8 (10.4 %) patients, while 4 (5.2 %) patients reported grade III-IV thrombocytopenia. Sixty-eight (88.3 %) patients visited a nurse regularly, and 22 (28.6 %) visited a nutritional therapist during CRT. Table 2 presents adverse events experienced by the patients.

Adjuvant immunotherapy with durvalumab

Following CRT, 22 (28.6 %) patients received adjuvant durvalumab therapy in 2020. During durvalumab adjuvant therapy, 10 patients (45.5 %) experienced immune-related adverse events (iAEs): grade 5 pneumonitis ($n = 1$), any grade pneumonitis ($n = 6$), and hypothyreosis ($n = 3$). Treatment was discontinued in 12 patients, 5 of whom had disease progression.

Subgroup comparison

There were no statistically significant differences between survival

Table 2
Treatment details and adverse events, 2016 vs. 2020.

Year	2016	2020
MDT meeting - n (%)	45 (84.9)	57 (74.0)
Time to treatment initiation from referral - months median	2.7	2.2
Radiotherapy		
CTV dose 60 Gy - %	27 (50.9)	47 (61)
CTV dose 66 Gy - %	16 (30.2)	14 (18.2)
CTV dose <60 Gy - %	8 (15.1)	9 (11.7)
PTV volume mean - cm^3	628.8	616.5
Heart mean dose - Gy	10.0	7.3
Ipsilateral lung mean dose mean- Gy	23.3	19.8
Contralateral lung mean dose	6.0	6.6
Chemotherapy		
Cisplatin (50 mg/m^2)-etoposide (Etoposide) (50 mg /m^2) - %	23 (43.4)	52 (65.4)
Weekly-paclitaxel (45 mg/m^2) - %	13 (24.5)	2 (2.6)
Carboplatin (45 mg/m^2)-Paclitaxel (AUC = 2) - %	9 (17)	12 (12.8)
Other - %	8 (15.1)	11 (1.3)
Chemotherapy administered as planned - %	34 (64.2)	51 (66.2)
Neoadjuvant treatment - %	16 (30.2)	12 (15.6)
Sequential treatment - %	6 (11.3)	4 (5.2)
Concurrent treatment - %	47 (88.7)	73 (94.8)
Operation after treatment - %	8 (15.1)	8 (10.4)
Adverse Events		
ECOG deterioration - %	18 (33.9)	26 (33.8)
Nausea - %	17 (32.1)	26 (33.8)
Coronary artery event - %	2 (3.8)	2 (2.6)
Grade III/IV esophagitis - %	1 (1.9)	2 (2.6)
Hospitalization due to infection - %	19 (35.8)	25 (32.5)
Weight loss above 5 kg - %	3 (5.7)	8 (10.4)
Anemia Grade III/IV - %	0	0
Anemia Grade II - %	6 (11.3)	12 (15.6)
Leucopenia Grade III/IV - %	6 (11.3)	8 (10.4)
Leucopenia Grade II - %	6 (11.3)	7 (9.1)
Thrombocytopenia Grade III/IV - %	3 (5.7)	4 (5.2)
Thrombocytopenia - Grade II % -	3 (5.7)	3 (3.9)
Regular visits to radiotherapy nurse - %	53 (100)	68 (88.3)
No regular visits to radiotherapy nurse - %	0	9 (11.7)
Visits to a nutritional therapist - %	19 (35.8)	22 (28.6)

Abbreviations: MDT, Multidisciplinary Team; CTV, Clinical tumor volume; PTV, Planning tumor volume; ECOG, Eastern Cooperative Oncology Group.

rates observed in 2016 and 2020. In univariate analyses of potential prognostic factors, patients treated sequentially were associated with shorter PFS than those treated concurrently (6 months [95 % CI 2.9–9.1] vs. 12 months [95 % CI 7.7–16.3]; $p = 0.07$). Regular visits to a nurse were associated with improved PFS (12.5 months [95 % CI 8.0–16.0] vs. 7 months [95 % CI 1.2–12.8] without regular visits to the nurse; $p = 0.016$). No statistically significant differences were detected in other subgroups or the OS between subgroups.

Discussion

Herein, a greater number of patients underwent CRT after guideline implementation, with 53 treated in 2016 and 77 in 2020. Thus, the use of CRT significantly increased by 45 %. Currently, there is no unified registry in Finland for collecting information on the number of patients diagnosed with stage III disease and those treated with radiotherapy or surgery annually. However, the overall lung cancer incidence has only slightly increased: 2734 patients in 2016 and 2801 patients in 2020, according to the 2020 Finnish Cancer Registry report. Moreover, one small central hospital radiotherapy unit lost patient data for 2020 due to a computer failure; hence, the number of patients who underwent CRT in 2020 may be higher. In 2020, the coronavirus 2019 (COVID-19) pandemic substantially impacted healthcare systems, possibly delaying the early diagnoses of NSCLC in Finland. Finally, the lack of national registries for stage III NSCLC treated patients limits the ability to accurately estimate the increasing proportion of patients receiving CRT.

Although patients had a better ECOG-PS in 2020, their disease stage was more advanced than that in 2016. Moreover, PD-L1 testing was increased, given that positive PD-L1 status is required for initiating adjuvant durvalumab treatment. Interestingly, patient cases were discussed less frequently in multi-disciplinary team (MDT) meetings, although clearly recommended in the established guidelines. In addition, regular visits to a radiotherapy nurse were arranged less frequently in 2020. Less frequent MDT meetings and fewer visits to a radiotherapy nurse could be attributed to COVID-19 restrictions in the clinics starting in the spring of 2020. The pandemic may have delayed the diagnoses of patients with lung cancer, leading to more advanced cancer stages. The use of platinum doublet chemosensitizer was more frequent in 2020, whereas neoadjuvant chemotherapy and sequential use of chemotherapy without concurrent chemotherapy were less frequently administered. The prevalence of surgical intervention after chemoradiation was slightly reduced in 2020. Furthermore, the proportion of patients who experienced >5 kg of weight loss increased slightly in 2020, along with the need for hospitalization. These findings could be attributed to the increased use of concurrent therapy with platinum doublet therapy as planned.

A new paradigm change has been introduced by adding adjuvant immunotherapy after CRT. In the PACIFIC trial, the addition of durvalumab markedly improved the results of conventional CRT [7]. In 2020, durvalumab was initiated in one-third of the patients, which is in line with other real-world data [13]. Regarding treatment-related AEs, we detected no new safety signals when compared with those in previous reports.

To compare the 2016 and 2020 patient groups, we performed survival analyses at the 2-year follow-up point for both study groups. The median PFS was 10 and 15 months in patients treated in 2016 and 2020, respectively, with no statistically significant difference between groups. Notably, PFS seemed to be inferior in patients treated sequentially. CRT has been shown to improve survival when compared with sequential chemoradiotherapy[14].Furthermore, regular visits to a radiotherapy

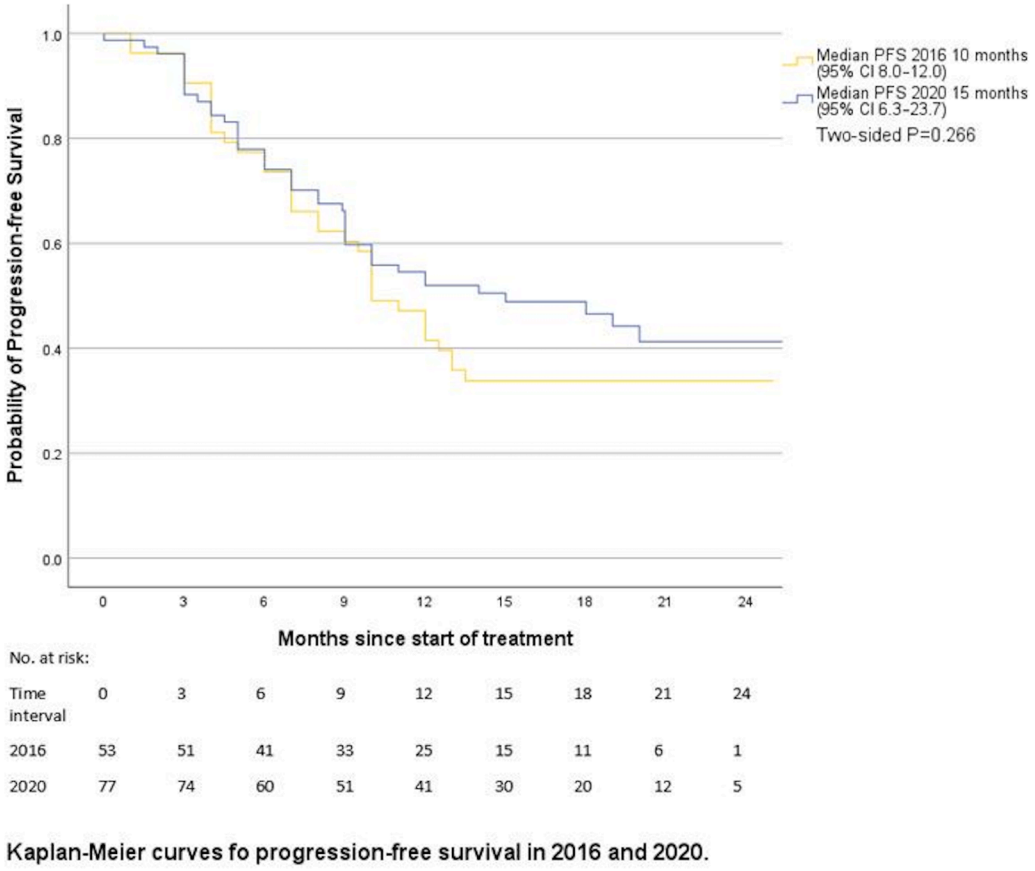

Fig. 1. Kaplan-Meier curves for progression-free survial in 2016 and 2020.

nurse were associated with improved PFS. CRT is a high-risk treatment, and regular supportive care for patients is crucial for completing the planned therapy, as well as adjuvant immune therapy. ESMO has published specific guidelines to improve supportive care during CRT [8]. The lack of statistical significance in most subgroups could be attributed to the relatively small sample size and the limited duration of follow-up in this study. These factors likely reduced the power to detect differences, particularly in subgroup analyses. Moreover, the stage shift observed between 2016 and 2020, with an increase in more advanced disease such as Stage IIIC, may have influenced the outcomes despite advancements in treatment and the introduction of durvalumab. An additional limitation is the retrospective design, which may have introduced selection and information biases; reliance on existing hospital records may also have led to underreporting or missing data. Furthermore, socioeconomic history was not systematically documented, limiting the ability to evaluate possible influences of social or economic background on treatment access or completion.

Despite the increased use of CRT, Finland lags behind other Nordic countries. For example, in Sweden, nearly 600 patients are diagnosed with stage III lung cancer annually, and approximately 50 % receive CRT. Considering that NSCLC accounts for approximately 85 % of lung cancer cases, and around 20 % of NSCLC patients are diagnosed with stage III disease, one would expect approximately 476 stage III NSCLC cases in Finland in 2020 based on national cancer incidence data. However, only 77 patients received CRT in 2020, corresponding to an estimated 16 %. This is notably low compared to the 50 % reported in Sweden. The high number of CRT-treated patients in Sweden could be attributed to the earlier diagnoses of patients with stage III. In addition, diagnostic processes are considered to be faster. For example, computed tomography can be performed at the primary healthcare level when lung cancer is suspected. In addition, sequential and induction chemotherapy prior to CRT are utilized more often in Sweden [15].

In conclusion, we successfully influenced clinical practice across the entire country by implementing therapy guidelines. The number of patients treated with CRT increased, compliance with the new guideline was good, and there was no uncontrolled inclusion of non-suitable patients in the newly formed treatment process.

Ethics statement

This retrospective study was conducted in accordance with the Declaration of Helsinki. Data were collected retrospectively with authorized permission from Findata. Due to the retrospective nature of the study and the use of pseudonymized data, the requirement for informed consent was waived. Ethical approval was obtained from the ethics committee at University of Turku, The Ethics Committee for Human Sciences at the University of Turku, Health care division approval 20 April 2020. Approval number (11/2020).

Data availability

The data that support the findings of this study are available from Findata, but restrictions apply to the availability of these data and are not publicly available. Data are however available from the authors upon reasonable request and with permission of Findata.

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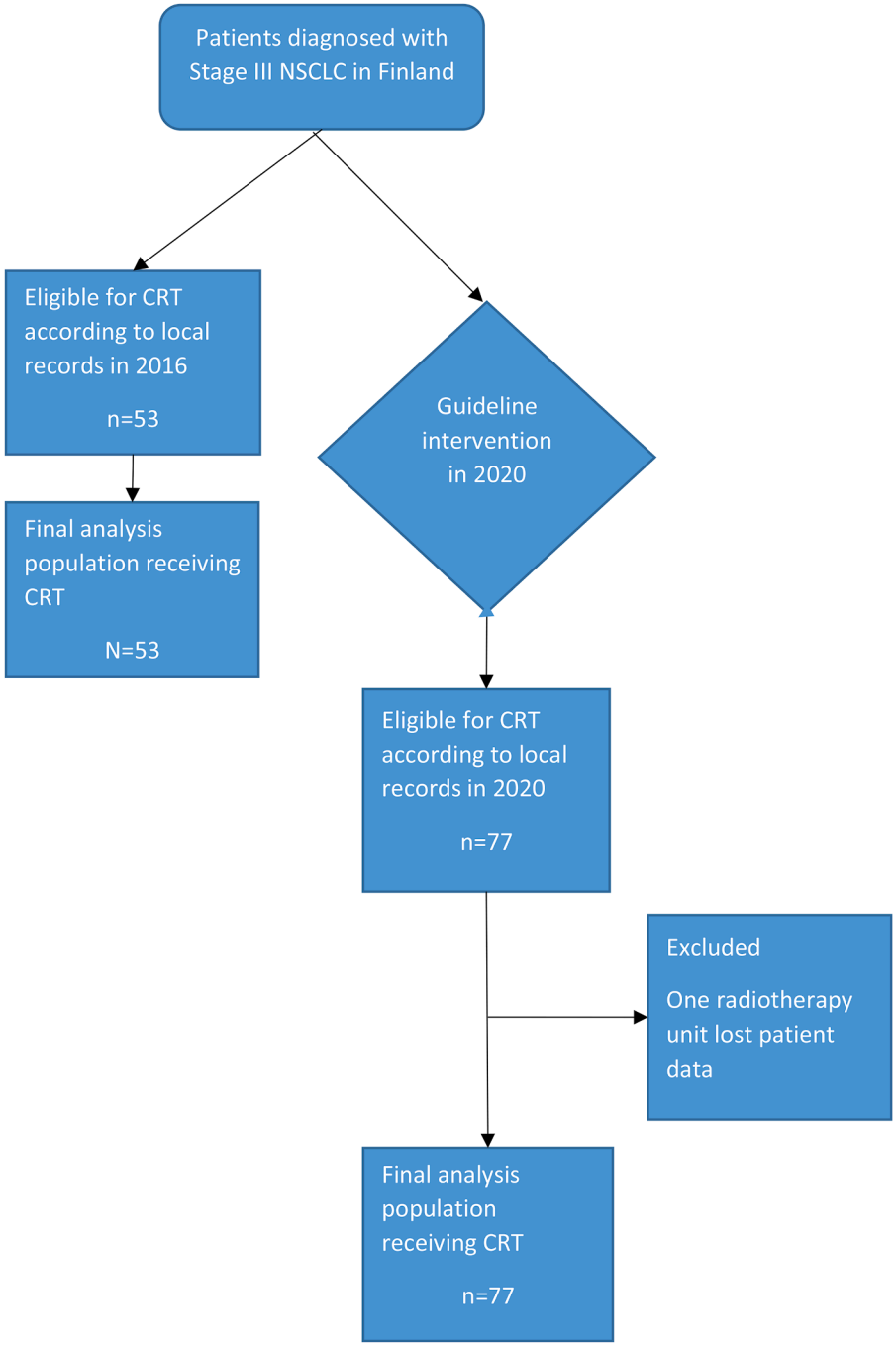

Flowchart.

CRediT authorship contribution statement

Viktor Wichmann: Writing – original draft, Investigation, Formal analysis, Data curation, Writing – review & editing. **Tanja Skyttä:** Investigation, Conceptualization, Formal analysis, Methodology. **Pekka Mali:** Investigation. **Anu Anttonen:** Investigation. **Kaisa Lehtiö:** Investigation. **Maria Tengström:** Investigation. **Auli Nevantaus:** Investigation. **Jenni Peltonen:** Investigation. **Liisa Sailas:** Investigation. **Mikko Myllykangas:** Investigation. **Elina Haalisto:** Investigation. **Juha Kononen:** Investigation. **Eliisa Löyttyniemi:** Formal analysis. **Antti Jekunen:** Supervision, Methodology, Funding acquisition, Conceptualization, Formal analysis, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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