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Research Article

Lung cancer reirradiation: Exploring modifications to utilization, treatment modalities and factors associated with outcomes

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ABSTRACT

Background: Patients treated for lung cancer (LC) often experience locoregional failure after initial treatment. Due to technological advances, thoracic reirradiation (re-RT) has become a viable treatment option. We sought to investigate the use of thoracic re-RT in LC patients over a time period characterized by technological advances in a large, multi-center cohort.

Methods and materials: LC patients treated with thoracic re-RT in two University Hospitals from 2010-2020 were identified. Clinical variables and RT data were extracted from the medical records and treatment planning systems. Overall survival (OS) was calculated from the last day of re-RT until death or last follow up.

Results: 296 patients (small cell LC n=30, non-small cell LC n=266) were included. Three-dimensional conformal radiation therapy was the RT technique used most frequently (63%), and 86% of all patients were referred for re-RT with palliative treatment intent. During the second half of the study period, the use of thoracic re-RT increased in general, more patients received curative re-RT, and there was an increased use of stereotactic body radiation therapy (SBRT). Median time between initial RT and re-RT was 18 months (range 1-213 months). Only 83/296 patients had combined treatment plans that allowed for registration of combined doses to organs at risk (OAR). Most of the combined doses to OAR were below recommendations from guidelines. Multivariate analysis showed superior OS ($p<0.05$) in patients treated with curative intent, SBRT or intensity modulated radiation therapy or had excellent performance status prior to re-RT.

Conclusions: The use of re-RT increased in the second half of the study period, although 2020 did not follow the trend. The use of SBRT and IMRT became more frequent over the years, yet the majority received palliative re-RT. Combined dose plans were only created for one third of the patients.

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Ethical approval: This study was approved by the Regional Committees for Medical and Health Research Ethics and the Norwegian Data Protection Officers at the involved hospitals. Informed consent was obtained from patients alive at the time of data collection, in patients who were already deceased, no consent was required.

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RÉSUMÉ

Contexte: Les patients traités pour un cancer du poumon (CP) connaissent souvent une défaillance locorégionale après le traitement initial. Grâce aux progrès technologiques, la réirradiation thoracique (re-RT) est devenue une option thérapeutique viable. Nous avons cherché à étudier l'utilisation de la réirradiation thoracique chez les patients atteints de cancer du poumon au cours d'une période caractérisée par des avancées technologiques dans une grande cohorte multi centrique.

Méthodologie et matériel: Les patients atteints de CP traités par re-RT thoracique dans deux hôpitaux universitaires entre 2010 et 2020 ont été identifiés. Les variables cliniques et les données de RT ont été extraites des dossiers médicaux et des systèmes de planification des traitements. La survie globale (SG) a été calculée à partir du dernier jour de la re-TR jusqu'au décès ou au dernier suivi.

Résultats: 296 patients (CP à petites cellules n=30, CP non à petites cellules n=266) ont été inclus. La radiothérapie conformationnelle tridimensionnelle était la technique de RT la plus fréquemment utilisée (63%), et 86% de tous les patients ont été orientés vers une re-RT avec une intention de traitement palliatif. Au cours de la seconde moitié de la période d'étude, l'utilisation de la RT thoracique a augmenté en général, plus de patients ont reçu une RT curative, et il y a eu une utilisation accrue de la radiothérapie corporelle stéréotaxique (SBRT). Le délai médian entre la radiothérapie initiale et la nouvelle radiothérapie était de 18 mois (de 1 à 213 mois). Seuls 83/296 patients ont bénéficié d'un plan de traitement combiné permettant l'enregistrement des doses combinées aux organes à risque (OAR). La plupart des doses combinées aux organes à risque étaient inférieures aux recommandations des lignes directrices. L'analyse multivariée a montré une meilleure SG (p>0,05) chez les patients traités avec une intention curative, une SBRT ou une radiothérapie avec modulation d'intensité, ou dont le statut de performance était excellent avant la nouvelle radiothérapie.

Conclusions: L'utilisation de la re-RT a augmenté dans la seconde moitié de la période d'étude, bien que l'année 2020 n'ait pas suivi la tendance. L'utilisation de la SBRT et de l'IMRT est devenue plus fréquente au fil des ans, mais la majorité des patients ont reçu une nouvelle radiothérapie palliative. Des plans de dose combinés n'ont été créés que pour un tiers des patients.

Keywords: Lung cancer; Re-irradiation; Reirradiation; Treatment patterns

Introduction

The treatment of lung cancer (LC) is typically multi-modal and may include radiation therapy (RT), surgery, chemotherapy, targeted therapies, and/or immunotherapy [1]. Treatment decisions are based on established guidelines as well as tumor- and patient-specific factors [2]. High-dose RT is often essential in the curative treatment of LC [3]. Thoracic re-irradiation (re-RT) is a subsequent course of RT that may be helpful in various scenarios [4]. LC can recur locally but may also metastasize to both lungs, pleura, ribs, and/or regional lymph nodes, where re-RT may be a relevant treatment option [1,5]. The likelihood of developing a second primary LC after undergoing curative treatment for LC is notably heightened as a result of preexisting smoking habits or a genetic predisposition [6]. Internationally, the number of LC patients treated with re-irradiation is increasing [7]. This increase is due to several factors, such as improved overall survival (OS), resulting in more patients being at risk of developing a late recurrence or a new primary tumor. Improvements in imaging techniques have resulted in a higher detection rate of new primary tumors or recurrent disease. This is attributed to the increased adoption of frequent surveillance, utilizing CT scans, following radical radiotherapy for non-small cell lung cancer (NSCLC) [8]. Additionally, there is a greater feasibility of re-RT delivery from improved RT technology allowing increased normal tissue sparing [9]. The enhanced survival rates among LC patients highlight the significance of improving the overall quality of life and alleviating the symptom burden associated with both early and late toxicities [10].

Achieving thoracic tumor control requires high RT dose delivery [11], which may be limited by the proximity to organs at risk (OAR), including the spinal cord, large vessels, main bronchus, heart, esophagus, and lungs [12]. Radiation-induced lung injury (RILI) is a common complication of thoracic radiation therapy [13-15] and includes a variety of pathologic pulmonary conditions with potentially fatal outcomes [15-17]. The risk of developing RILI depends upon the patient's underlying comorbidities, tumor characteristics, additional treatment, RT dose, and treatment technique [11,18,19]. The risk of RILI is directly related to the volume of irradiated lung and the mean lung dose [15,16,19]. The choice of RT technique may affect the dose received by surrounding healthy tissue [20,21]. Intensity-modulated radiation therapy (IMRT) achieves optimal conformal dose distribution around the target volume compared to three-dimensional conformal radiation therapy (3D CRT), which may impact both high and low radiation doses to OARs [22]. The treatment of small lesions, such as small primary lung tumors (typically <5-7 cm), may be performed using stereotactic body radiation therapy (SBRT), a highly conformal RT technique delivering high radiation doses in a few fractions [23]. Data suggests that the risk of RILI decreases with the use of more conformal RT techniques such as IMRT, SBRT, and proton therapy [15,17,19,24]. Diagnosis-specific guidelines provide dose-volume recommendations aiming to decrease lung toxicity [10], as severe RILI has a significant impact on the patient's quality of life and their ability to perform daily activities. Thoracic re-RT is performed in curative and palliative settings, and will increase the total lung dose.

Therefore, achieving the dual objectives of minimizing the risk of RILI and other side effects while maximizing the tumor dose may seem conflicting. Addressing this opposition is critical, as it affects morbidity, local tumor control, and overall survival (OS) [11].

While there are published reports on the safety and efficacy of thoracic re-irradiation [5,25-32], there is a lack of guidelines for patients undergoing re-irradiation in the thoracic region [1,28]. Therefore, clinical decisions such as the preferred RT technique, fractionation regimen, and cumulative dose constraints have often been left to the discretion of the treating physician and available technical measures [5,9,27,33]. Thus, it is relevant to investigate the impact of various thoracic re-RT strategies on the dose delivered to target volumes and OARs. This study aimed to analyze the use of thoracic re-RT in LC patients and explore factors associated with OS after thoracic re-RT, delivered between 2010-2020 at two Norwegian hospitals.

Methods and materials

Participants

Researchers retrospectively reviewed all LC patients that received thoracic re-RT at University Hospital of North-Norway and Oslo University Hospital from 2010-2020. Follow up appointments concluded by June 18th, 2021. Patients who underwent initial RT and re-RT treatments at the same clinic were identified through the hospital register. The inclusion criteria comprised of individuals aged 18 or older, initially treated with RT for any cancer diagnosis in the thoracic region, and subsequently undergoing a new course of RT in the thorax specifically for LC. Patients included in the study were considered to have either recurrent, metastatic, or new primary LC, although in many cases, information in the medical records were not clear. This study involves patients who received a repeated course of treatment in the same area, where some degree of dose overlap occurred due to the treatment fields overlapping with the previously irradiated volume. This volume could be situated within the planned target volume (PTV) or the OARs. Patients treated with a new course of RT with concerns of toxicity due to the total RT burden, but without overlapping treatment fields were also included [4]. Patients receiving treatment for bone metastases and lesions treated with electrons were excluded. Demographic and clinical data such as age, comorbidity, histology, Eastern Cooperative Oncology Group (ECOG) performance status at the time of re-RT, and information on systemic therapy given within one month before and after re-RT, was collected from the electronic medical records. The treatment intent at the time of re-RT was considered curative for patients who received a physical dose exceeding 40 Gy, regardless of the fraction size [34]. Patients treated with a physical dose of 40 Gy or lower were considered palliative intent. RT treatment data such as fractionation schemes and RT techniques were collected from the electronic medical records and treatment planning systems.

Patients were grouped into two cohorts according to IMRT availability in the clinics; 2010-2014 (some availability of IMRT) and 2015-2020 (full availability of IMRT) [34].

After re-RT, the OS was defined as the time between the last re-RT fraction and the death date or end of follow-up, June 18th, 2021.

Radiation treatment planning and delivery

All patients had treatment plans based on a 3D or 4D RT planning CT. Treatment planning was performed in Oncentra Masterplan v.4.5.3 (Elekta, Stockholm, Sweden), Raystation v.9.a (Raysearch, Stockholm, Sweden), or Eclipse v.15.0 (Varian, Palo Alto, California, USA).

Dosimetric information, comprising both the initial RT plan and the re-RT plan, was gathered from the treatment planning system. This combined dose data was available for 83 patients. The combined plans were formulated before re-RT and computed using either deformable or rigid registration. Deformable registration was exclusively available in Raystation. Once the plans were combined, the mean heart dose (MHD), mean lung dose (MLD), and lung volume receiving 5 Gy (V5Gy) and 20 Gy (V20Gy) were documented for analysis. The proportion of patients who had a combined lung and heart dose under the recommended levels described by the Norwegian Lung Cancer Group [2] were calculated. Lung doses were collected from the total lung volume or total lung volume minus gross tumor volume. In the 83 patients with combined plans, treatment fields were visualized and noted as overlapping or not. In 213 of the included patients (72%), a combined plan from the initial RT and re-RT was lacking. Therefore, dose plan documentation and medical records were used to consider if the re-RT treatment plan had overlapping treatment fields with the initial treatment plan.

During the initial course of RT, patients were treated according to guidelines from the Norwegian Lung Cancer Group [35-37], although the national guidelines do not describe thoracic re-RT [35-37]. Guidelines from the European Society of Radiation Therapy and Oncology (ESTRO), the European Organization for Research and Treatment of Cancer (EORTC) on re-irradiation [38], and the consensus guideline by Rulach and colleagues [9] were not published until after the study period. Thus, fractionation, re-RT technique, and dose constraints were determined for every patient individually by the clinician.

A variety of linear accelerators with energies ranging from 4 MV to 15 MV were used for treatment delivery. Execution of image guidance was performed in accordance with the local protocols, which were derived from the margins applied in the treatment plans. The equivalent dose in 2 Gy fractions (EQD2) for target doses to the tumor was computed using the EQD2 formula, incorporating a tumor α/β-value of 10 Gy.

Statistical analysis

Descriptive statistics summarizing patient characteristics were analyzed using SPSS® (v.27). Overall survival (OS) was an-

alyzed and compared for patients who received re-RT within six months versus those who received re-RT after a period longer than 6 months following the initial RT course. This distinction is based on the suggested minimum recommended interval of 6 months between RT courses [9]. OS was estimated using the Kaplan-Meier method. The comparison of OS in LC patients undergoing re-RT was conducted based on clinical and treatment-related factors outlined in Table 2. The analysis utilized the log-rank test and Cox regression analysis. Data with $p < 0.05$ were considered statistically significant. Variables included in the multivariate Cox regression were examined for collinearity with variance inflation factor < 3 for all variables.

Ethics

This study was approved by the Regional Committees for Medical and Health Research Ethics (reference no.117365) and the Norwegian Data Protection Officers at the chosen hospitals (reference no.20/17916 and 02754). Informed consent was obtained from patients alive at the time of data collection. No consent was required for patients who were since deceased.

Results

Two hundred ninety-six LC patients were included in the analysis. Demographics, treatment-related characteristics, and OS after re-RT is shown in Table 1. Sixty-five percent of patients were treated at Oslo University Hospital and 35% at University Hospital of North-Norway. Most patients (90%) were diagnosed with non-small cell lung cancer (NSCLC), with the remaining 10% receiving treatment for small cell lung cancer (SCLC). The median age at re-RT was 67 years (range 29-92 years), the median time interval between initial RT and re-RT was 18.4 months (range 1 to 213 months).

In this study, the overall median initial RT target dose was 42 Gy (EQD_2=44.8 Gy), and the median re-RT target dose was 24.5 Gy (EQD_2=29.7 Gy). The combined dose from initial RT and re-RT ranged from 20-121 Gy (EQD_2=33.3-252 Gy) (Table 2). Overlap between the re-RT and previously treated volumes was recorded in 210 (71%) patients (Table 1). The average number of LC patients treated with re-RT per year increased from 15 in 2010-2014 to 37 in 2015-2020 (Fig. 1A).

In total, 254 (86%) of re-RT patients were treated with palliative intent (Table 3). One hundred and eighty-four of these palliative patients (72%) were treated with 3D CRT, while 29 patients (12%) were treated with IMRT (Fig. 2). Eight out of 42 curative-intent patients were treated with IMRT, and 2 curative intent patients were treated with 3D CRT (Fig. 2). The remaining 41 palliative and 32 curative patients were re-treated with SBRT (Fig. 2). The use of SBRT increased over the study period and accounted for 12% of patients treated from 2010-2014 and 29% of the patients in 2015-2020 (Fig. 1B). Fig. 1A illustrates the increased number of curative intent re-RT from 10 to 32 between 2010-2014 to 2015-2020, respectively. There was also increased use of palliative IMRT, from 2 patients in 2010-2014 to 27 patients in 2015-2020, whereas the use of palliative 3D CRT dropped from 59/67 patients (88%) in 2014-2015 to 125/187 (67%) during 2015-2020 (Fig. 2).

Data for combined doses from initial and re-RT delivered to the heart and lungs are shown in Table 2. For 89% of the patients with estimated lung doses, a lung V20Gy less than 35% were identified. In the patients where V20 Gy values exceeded 35%, the values raged up to 40%. The estimated combined MLD in 76 out of 83 patients (92%) was below 20 Gy. The combined V5Gy was below 65% in more than two thirds (77%) of the patients. For the remaining patients, where the lung V5Gy surpassed 65%, the V5Gy were up to 85%. The estimated combined MHD had a median value of 6 Gy, varying between 0 and 40 Gy, 93% of the patients had a combined MHD of less than 35Gy (Table 2).

A total of 233 patients (79%) were alive 3 months after completing re-RT (Table 1). The only factors associated with a difference in OS ($p<0.05$) in the multivariate analyses were treatment intent, showing inferior OS for palliative intent patients with hazard ratio of 2.9 (CI 1.6-5.1), ECOG performance status showing superior OS in ECOG 0 patients (HR 1.0, reference) compared to ECOG 2 (HR 2.4, CI 1.4-3.3), and 3-4 (HR 6.1, CI 4.8-10.2). Superior OS was seen in patients treated with an IMRT technique with HR 0.6 (CI 0.4-0.9), and SBRT with HR 0.4 (CI 0.2-0.6) (Table 3).

Discussion

This study aimed to analyze the use and strategies of thoracic re-RT and its impact on RT doses and association with survival in a large multi-center cohort of 296 LC patients treated with re-RT from 2010 to 2020 at Oslo University Hospital and University Hospital of North-Norway. The majority of patients were treated with 3D CRT (63%), and treatment intent was most commonly palliative (86%). The use of re-RT increased after 2014, and the techniques applied in the second half of the study period were trending towards increased use of SBRT, more frequent palliative IMRT, and less frequent palliative 3D CRT. Factors independently associated with a significant increase in OS include curative treatment intent, treatment with IMRT or SBRT technique, and low ECOG performance status.

The risk of severe radiation-induced toxicity may limit the target dose, thus there are several factors to consider when balancing the risks and benefits of re-RT, however evidence-based guidelines are scarce. A study by Rulach and colleagues [9] aimed to reach a consensus on treatment guidelines for re-RT of NSCLC by inviting experienced LC oncologists to answer questions related to treatment decisions. The expert survey was published in 2021, and therefore, was not available to guide treatment decisions related to patients in our study. However, recommendations will be highlighted to identify to which degree the LC re-RT in our clinics were in line with these consensus statements [9].

A challenge affecting decisions related to re-RT is the limited knowledge of the true tolerance of OARs [5]. Time elapsed from initial RT to re-RT can allow for a degree of tissue recovery

Table 1
Demographic and clinical data in lung cancer patients (n=296) treated with re-RT.

	n= (%)
Sex	
Male	159 (54)
Female	137 (46)
Histology	
SCLC	30 (10)
NSCLC	266 (90)
NSCLC Adenocarcinaoma	*97 (37)*
NSCLC Squamous cell carcinoma	*67 (25)*
NSCLC Other/not specified/unknown	*102 (38)*
Age at re-RT: median (years) [min,max] (±SD)	67 [29, 92] (±10.9)
Months between initial RT and re-RT: median [min,max] (±SD)	18.4 [0.7, 212.9] (±28.9)
Follow-up in months after re-RT in patients alive at end of follow-up: median[min,max] (±SD)	27.5 [5.6, 92.8] (±34.0)
Patients alive 3 months post re-RT	233 (79)
ECOG at re-RT	
0	54 (18)
1	145 (49)
2	69 (23)
3	27 (9)
4	1 (1)
Comorbidity at time of re-RT	
No	58 (20)
Yes	238 (80)
Cardiovascular disease	50 (21)
Hypertension	3 (1)
Chronic obstructive pulmonary disease	35 (15)
Other pulmonary disease	2 (1)
Other primary cancer	18 (8)
Other comorbidity; motor neuron disease, HIV, multiple sclerosis, severe renal failure	4 (1)
Comorbidity combination	127 (53)
Symptoms at time of re-RT	
No	95 (32)
Yes	201 (68)
Cough	12 (6)
Dyspnea	95 (47)
Thoracic pain	36 (18)
Combination of symptoms	58 (29)
Systemic therapy one month before/after re-RT	
No	221 (75)
Yes	75 (25)
RT technique	
3D-CRT	186 (63)
IMRT	37 (12)
SBRT	73(25)
Overlap	
Yes	210 (71)
No	86 (29)

Abbreviations: n=number, SD= Standard Deviation, SCLC=Small Cell Lung Cancer, NSCLC=Non-Small Cell Lung Cancer, min=minimum, max=maximum, re-RT=reirradiation, RT=radiation therapy, ECOG PS=Eastern Cooperative Oncology Group Performance Status, HIV= Human Immunodeficiency Virus, 3D CRT=Three-Dimensional Conformal Radiation Therapy, IMRT=Intensity Modulated Radiation Therapy, SBRT=Stereotactic Body Radiation Therapy.

[39], although the extent of which is currently not well defined for thoracic OARs. In a systematic review of 1,243 thoracic re-RT patients performed by Maddalo and colleagues [25], the median interval between initial and re-RT among patients with LC or thoracic metastases was 18 months. At the same time, a smaller study by Schröder and colleagues [5] that included LC, esophageal, and various metastatic cancers reported a 14-month median interval. Similar results of a median interval of 18 months (Table 1) were found in our study.

In the work of Rulach and colleagues [9] no consensus was met on the minimum recommended interval between initial RT and re-RT; however, most oncologists (73%) agreed that a 6-month interval was minimum in radical re-RT [9]. A majority (82%) of the patients included in the current study were treated with more than 6 months between the initial and re-RT courses. However, a total of 53/296 LC patients were re-irradiated with less than 6 months interval in our study. The median OS of patients treated $\leq$ 6 months interval was nearly

Table 2
Doses to target and organs at risk.

	No of patients	Median target nominal dose [min, max]	Median target EQD2 dose [min, max]	Median MLD Gy [Min, max] Proportion MLD <20Gy	Median lung V20Gy [Min, max] Proportion V20Gy <35%	Median lung V5Gy [Min, max] Proportion V5Gy <65%	Median MHD Gy [Min, max] Proportion MHD <35Gy
Initial RT dose all patients	296	42.0 [8, 70]	44.8 [12, 126]				
Re-RT dose all patients	296	24.5 [8, 70]	29.7 [12, 126]				
Combined doses in all patients	296	66.5 [20,121]	76.2 [33.3, 252]				
Initial RT dose in patients with combined plans	83	45 [8.0, 66.0]	50.0 [12, 126]	6.0 [0.6, 33.2]	0.8 [0.0, 45.1]	31.4 [2.8, 98.2]	2.6 [0.0, 33.9]
Re-RT dose in patients with combined plans	83	42 [9.0, 70.0]	43.2 [16, 126]	3.9 [0.3, 26.9]	3.2 [0.0, 70.2]	21.1 [0.7, 99.3]	2.4[0.0, 20.6]
Combined doses in patients with combined plans	83	81.0 [34.0, 120.0]	131.3 [46.1, 222.3]	11.1 [2.6, 53.9] 89%	14.5 [1.3, 40.0] 92%	39.5 [9.8, 85.4] 77%	5.7 [0.1, 40.3] 93%
Initial RT dose in patients lacking combined plans	213	39.0 [8.0, 70.0]	42.3 [12, 126]				
Re-RT dose in patients lacking combined plans	213	20.0 [8.0, 68.0]	26.2 [12, 126]				
Combined RT dose in patients lacking combined plans	213	62.0 [20.0, 121.0]	70.8 [33.3, 252]				

Abbreviations: Min=Minimum, max=Maximum, EQD2=Equivalent dose in 2 Gray fractions, V=Volume, Gy= Gray, MLD=Mean lung dose, MHD=Mean heart dose

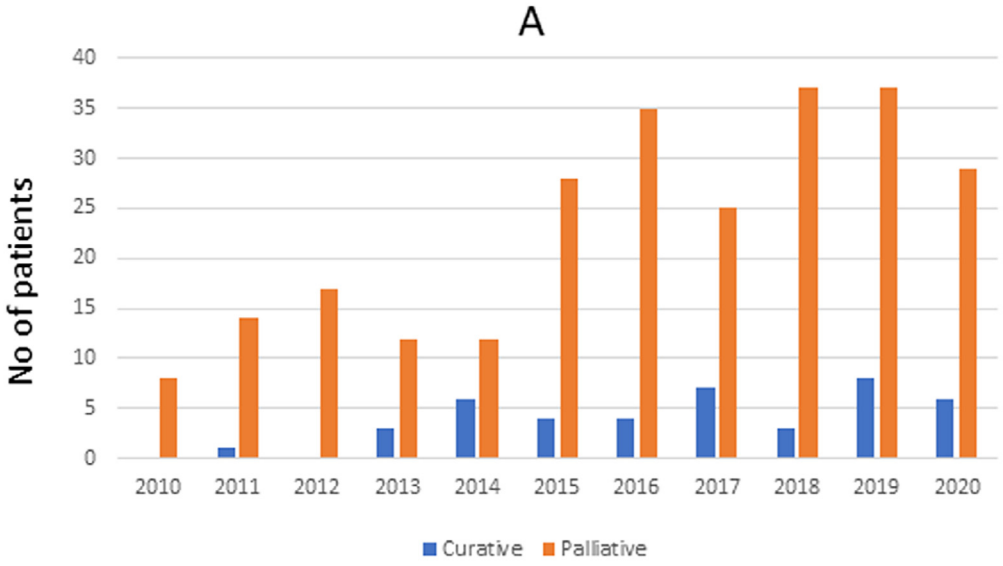
4 months shorter than the median OS found in the patients treated with more than 6 months interval (6.7 months vs. 10.4 months) (Table 3) These findings suggest that in patients needing short interval re-RT, which was most commonly for palliative intent, survival was typically limited. However, a short interval between initial RT and re-RT may also indicate the nature of aggressive and progressive LC and/or lack of other treatment options for those patients. For evaluating the degree of overlap and combined doses to OAR, Rulach and colleagues [9] and Drodge and colleagues [33] present recommendations of combining plans of initial and re-RT with rigid or deformable registration for patients with both curative and palliative intent. This was only done in 83/296 LC patients (Table 2), while the remaining 213 patients had no quantitative data on combined doses to OAR. Reasons for this might include the use of several different treatment planning systems between 2010-2020, or that a manual evaluation of combined initial and re-RT OAR doses was performed. Additionally, the procedure to calculate a combined treatment plan is challenging and highly uncertain since major anatomical changes can occur from the initial treatment to the time of re-irradiation. In such cases, documentation, and communication of risk assessment for the individual patient remains a challenge. However, among the 83 patients where a combined plan was calculated, 92% of the patients received V20Gy lung >35% (Table 2), which is stricter thanthe suggested dose constraint of V20Gy >40% in combined plans by the American Radium Society and American College of Radiology [40]. 89% of the patients had an estimated combined MLD >20Gy (Table 2), which is stricter than the suggested dose constraint of MLD >22Gy by Troost and colleagues [41].

Nieder and colleagues [42] in 2013 found an increase in highly cited articles about re-RT, and our results show an increase in the use of re-RT in the second half of the study period (Fig. 1A). This finding could be a result of more technically advanced and effective treatment as suggested by Armstrong and Hoskin [43]. The year 2020 might not be representative for the trend of an increasing number of patients treated with re-RT due to the COVID-19 pandemic. Studies have reported a significant decrease in the number of patients in the RT-clinics in 2020 compared to 2019 [44,45] Results also show a decrease in the total number of LC patients from 45 in 2019 to 35 in 2020 (Fig. 1A). In a study by Fornacon-Wood and colleagues among 12,499 LC patients treated with thoracic RT from 2005 to 2020, the proportion of curative intent RT increased after the introduction and routine use of IMRT [34]. The results of the current study can confirm similar trends, although the differences in curative versus palliative intent between time groups are less obvious in our study. The data in the study of Fornacon-Wood and colleagues [34] were only related to initial RT and

Table 3
Demographic data and survival after re-RT completion for 296 lung cancer patients.

Variables	Number (%)	Median survival in months from re-RT [min, max] (95% CI)	Mean survival in months from re-RT [±SD] (95% CI)	Log rank	Cox regression†					
					Univariate			Multivariate		
				P	HR	95%CI	*P*	HR	95%CI	*P*
All patients	296 (100)	9.6 [0.0-121.0] (7.4-11.8)	24.5 [±2.5] (19.6-29.3)							
Sex				.228						
Male	159 (54)	9.0 [0.0, 121.0] (6.0-11.9)	22.5 [±3.2] (16.2-28.9)		1.2	0.9-1.5	.229			
Female	137 (46)	10.3 [0.1, 92.8] (7.2-13.4)	23.7 [±2.7] (18.4-29.1)		Ref					
Comorbidity				.075						
Yes	238 (80)	9.3 [0.0, 121.0] (6.9-11.6)	22.1 [±3.0] (17.4-26.9)		1.4					
No	58 (20)	12.4 [0.1, 80,2] (7.3-17.4)	28.3 [±4.4] (19.7-36.9)		Ref	1.0-1.9	.076			
Overlap				<.000			<.000			
Yes	210 (71)	7.1 [0.0, 121.0] (5.6-8.6)	20.4 [±2.7] (15.1-25.7)		1.9	1.4-2.6		1.1	0.8-1.6	.584
No	86 (29)	20.6 [0.4, 84.7] (16.1-25.1)	30.6 [±3.6] (23.6-37.6)		Ref			Ref		
Treatment intent				<.000			<.000			
Curative	42 (14)	*	60.6 [2.0, 92.8]		Ref	3.1-8.9		Ref	1.6-5.1	.000
Palliative	254 (86)	-7.4 [0.0, 121.0] (6.0-8.8)	(48.4-72.9)		5.2			2.9		
			17.1 [±1.9]							
			(13.3-20.8-17.4)							
Age				.368						
≤65 years at re-RT	107 (36)	11.0 [0.3, 80.2] (5.7-16.3)	22.7 [±3.3] (15.1-28.1)		0.9	0.7-1.2	.369			
>65 years at re-RT	189 (64)	9.2 [0.0, 121.0] (6.8-11.7)	22.5 [±2.8] (18.7-29.6)		Ref					
Systemic therapy 1 month				.432						
before/after re-RT	75 (25)	10.3 [0.1, 121.0] (4.2-16.4)	29.9 [±6.4] (19.6-40.2)		Ref	0.8-1.5	.433			
Yes	221 (75)	9.6 [0.0, 92.8] (7.2-11.9)	20.7 [±2.0] (16.8-24.7)		1.1					
No										
Time between initial RT				.391						
and re-RT	53 (18)	6.7 [0.3, 80.2] (5.1-8.3)	18.9 [±3.5] (12.0-25.7)		0.9	0.6-1.2	.391			
≤6 months	243 (82)	10.4 [0.0. 121.0] (7.9-12.9)	25.8 [±2.8] (20.4-31.2)		Ref					
>6 months										
ECOG functional status				.000						
0	54 (18)	20.6 [0.1, 92.8] (12.0-29.3)	32.3 [±4.8] (22.9-41.7)		Ref	0.9-1.9	<.000	Ref	0.9-2.0	.000
1	145 (49)	13.5 [0.0, 121.0] (9.7-17.3)	27.9 [±4.7] (20.4-35.4)		1.3	1.6-3.6	.179	1.4	1.4-3.3	.066
2	69 (23)	6.4 [0.3, 58.7] (5.1-7.6)	11.1 [±1.7] (7.8-14.4)		2.4	2.8-7.7	<.000	2.4	4.8-10.2	.000
3-4	28 (10)	2.9 [0.1, 48.4] (1.8-4.0)	6.0 [±2.2] (1.7-10.3)		4.6		<.000	6.1		.000
RT technique at re-RT				<.000						
3D-CRT	186 (63)	6.0 [0.0, 73.8] (5.0-7.0)	11.2 [±1.2] (8.9-13.4)		Ref	0.3-0.7	<.000	Ref	0.4-0.9	.000
IMRT	37 (13)	10.2 [0.3, 121.0] (0.0-25.4)	38.0 [±9.1] (17.1-52.9)		0.5	0.2-0.3	.001	0.6	0.22-0.6	.021
SBRT	73 (25)	35.2 [2.0, 92.8] (28.6-41.8)	45.0 [±4.4] (36.3-53.7)		0.2		<.000	0.4		.000

Abbreviations: re-RT= reirradiation, RT= radiation therapy, min= minimum, max= maximum, CI=confidence interval, SD= standard deviation, HR= hazard ratio, ECOG= Eastern Cooperative Oncology Group, 3D-CRT= three-dimensional conformal radiation therapy, IMRT= intensity modulated radiation therapy, SBRT= stereotactic body radiation therapy, Gy= Gray †Multivariate cox regression analysis was performed with variables with p-value <.05 in univariate analysis. * Median OS values not available from Kaplan Meier metho



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
Curative	0	1	0	3	6	4	4	7	3	8	6	42
Palliative	8	14	17	12	12	28	35	25	37	37	29	254
Total	8	15	17	15	18	32	39	32	40	45	35	296

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
SBRT curative	0	1	0	2	1	5	4	4	4	6	6	33
SBRT palliative	0	1	1	1	2	3	7	6	8	8	3	40
SBRT Total	0	2	1	3	3	8	11	10	12	14	9	73

Figure 1. (A) Number of LC patients treated with curative and palliative re-RT from 2010-2020. (B) Number of LC patients treated with SBRT technique from 2010-2020 by treatment intent.

did not include patients treated with a second course of RT. Therefore the relatively inferior prognosis of patients requiring re-RT could explain the difference seen in our study compared to those reported by Fornacon-Wood and colleagues. On the other hand, the use of SBRT increased from 9 patients in 2010-2014 to 64 patients in 2015-2020 (Fig. 2). Also, the use of IMRT in palliative re-RT, increased from 2 patients to 27 patients from 2010-2014 versus 2015-2020 (Fig. 2). This finding indicates an increased use of high-dose re-RT with IMRT and SBRT in the involved clinics. These findings are also in ac-

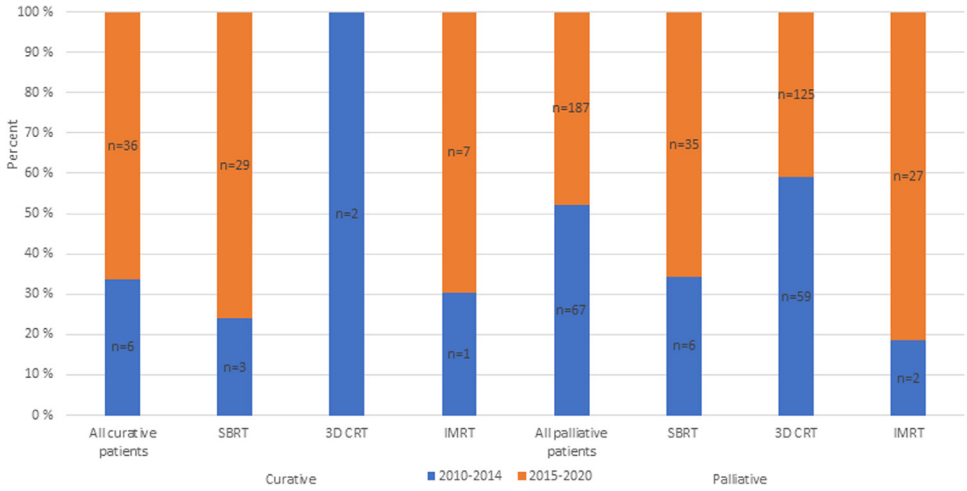


Figure 2. The distribution of RT technique in 2010-2014 (n=73) and 2015-2020 (n=223) by treatment intent.

cordance with the recommendations published by Rulach and colleagues, suggesting the use of highly conformal techniques in radical re-RT [9]. In the current study, re-RT with SBRT was used in 25% of cases (Table 3), which is lower than 52.4% of re-RT in their small cohort of 42 patients reported by Schröder and colleagues [5]. However, an inclusion criterion from the study of Schröder and colleagues [5] was a prescription dose at or higher than 50 Gy in an equivalent dose of 2 Gy fraction dose, which excludes the palliative intent patients that predominated the current study. In palliative intent re-RT, Beddok and colleagues [46], and Drodge and colleagues [33] suggest that all re-RT should be performed using a conformal technique minimizing OAR dose. The present study reports a total of 41 out of 254 and 32 out of 42 treated with palliative and curative treatment intent respectively, received re-RT with SBRT (Fig. 2).

ECOG performance status has been found to be a prognostic factor in thoracic re-RT [33]. Both Rulach and colleagues [9] and Drodge and colleagues [33] recommend ECOG $\leq$2 for radical re-RT but do not provide ECOG recommendations in palliative re-RT [33]. Our results show that only 10% of LC patients had ECOG 3 or 4 prior to re-RT (Table 3).Avoiding re-RT was a general recommendation [9] for patients with interstitial lung disease. Among the LC patients in our cohort, 80% had one or more comorbidities, and although details of the comorbidities were not provided, the etiology of LC indicates that lung comorbidities are likely to be found among those patients.

Median OS among palliatively RT-treated LC patients was approximately 5 months in a literature review performed by Drodge and colleagues [33]. This finding is consistent with the median survival of 6 months in this group in the current study (Table 3). In our study, factors found to be significantly ($p<0.05$) associated with OS in the multivariate analysis were treatment intent, RT technique, and ECOG performance status. These factors are likely interrelated, given that palliative intent radiotherapy (RT) is commonly administered using 3D conformal radiotherapy (3D CRT) and prescribed with a lower target dose, especially in patients with limited performance status. Our findings also correspond with the results of Käsmann and colleagues which showed superior OS in SCLC patients with good performance status treated with re-RT dose >40 Gy [47], although in our cohort, the proportion of SCLC patients was small.

Limitations

There are several limitations to this retrospective study. A combined plan for the two treatments existed for only a small proportion of the patients. Additionally, the retrospective design of this study does not provide information on early or late toxicities from re-RT, as follow-up was done in the patients' local hospitals. Evaluation of the effect of re-RT should be carefully interpreted in patients who were also treated with other oncologic modalities. The study, unfortunately, has no access to information related to the cause of death in the deceased patients. Survival outcomes between the SCLC and NSCLC patients were not calculated as the number of SCLC patients was small. Additionally, disease stage of LC was not included in our study, and therefore our results do not provide information related to this issue. Doses > 40Gy may not be enough to be curative and represents an uncertainty of our results, however no consensus on curative dose in re-RT have been set [38] Also, the numbers collected from the year 2020 might have been influenced by the Covid-19 pandemic, and may not be representable for the trend of an increasing number of LC patients treated with re-RT the previous years. Notably, however, this study provides detailed information on the treatment of thoracic re-RT in a geographical area covering more than half of Norway's population over more than a decade's time.

Conclusion

The use of re-RT with both palliative and curative intent were used more frequently in the second half of the study period as SBRT and IMRT became more frequent techniques in use.

Calculated estimations of combined doses to OAR existed in less than one of three patients. Three months survival was 79% and factors independently associated with differences in OS were treatment intent, treatment technique and performance status. Future research should analyze dosimetric data in relation to patient reported outcome measures before and after re-RT.

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