Graduate thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

Arththi Shanmugam, Bjørn H. Grønberg, Marie S. Sandvei

Stereotactic Body Radiation Therapy at St. Olav's Hospital

Graduate thesis in Programme of Professional Study, Medicine
Supervisor: Bjørn H. Grønberg
Co-supervisor: Marie S. Sandvei

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Abstract

Introduction

Stereotactic body radiation therapy (SBRT) is a widely used curative treatment alternative for early-stage NSCLC which has been available at St. Olav's Hospital since 2006. In this retrospective study, we have assessed the outcomes of patients treated with SBRT at our institution in order to investigate whether outcomes differ from results reported by international colleagues.

Methods

We retrieved a list of all patients who have undergone SBRT from the administrative system at our radiotherapy department since 2007. We excluded patients treated in 2006 since this was the start-up period for SBRT. Data were collected from each patient's hospital medical records. The 8th edition of the TNM classification system was used for staging of disease, and response was evaluated according to the RECIST 1.1. Survival was estimated using the Kaplan Meier method, and the Cox proportional hazard method was used for the multivariable analyses adjusting for baseline and disease characteristics.

Results

We identified 226 patients treated with SBRT at our institution from 2007 to 2019. Last follow-up date was set to June 30th, 2020. Median age was 74 years, and the group had a median Charlson Comorbidity Index score of 2 points. 23.9% achieved a complete response, 36.3% a partial response whereas 20.8% had stable disease and 1.3% progressed. Median OS was 40.7 months, and 1-year, 2-year and 5-year survival rates were 86%, 66% and 39%, respectively. 1-year and 5-year progression free survival rates were 72% and 37%, respectively. Only a marginal reduction in lung function was found (-0.1 L in FEV1 and -0.4% in FEV1%) and few reported side effects; most common were dyspnoea (4.4%), chest pain (3.1%), skin reaction (2.7%) and costal fracture (2.7%). Eventually, 12.4% had local relapse, 15.5% were diagnosed with a new primary tumor and 15.5% developed metastases, most commonly in the skeleton/muscle (5.8%), brain (5.3%) and liver (4.9%). 50.7% died relapse free and 23.9% died of their lung cancer.

Conclusions

Our study shows that SBRT was well tolerated, and disease control and survival after treatment was similar to what has been reported by other investigators. SBRT appears to be a safe and effective treatment alternative for medically inoperable patients.

Abstrakt

Introduksjon

Stereotaktisk strålebehandling er et velkjent kurativt alternativ for tidlig-stadium NSCLC, som har vært tilgjengelig ved St. Olavs Hospital siden 2006. I denne retrospektive studien, har vi analysert utfallene hos pasienter behandlet med stereotaksi ved vår institusjon for å undersøke nærmere om utfallene avviker fra resultater rapportert i internasjonale studier.

Metoder

Vi hentet en liste over alle pasienter som har gjennomgått stereotaksi siden 2007 fra det pasient-administrative systemet ved stråleterapiavdelingen ved St. Olavs Hospital. Vi ekskluderte pasientene behandlet i 2006, siden dette var oppstartsperioden for stereotaksi. Data ble samlet inn ved å gå gjennom sykehusjournalen til hver enkelt pasient. 8. utgave av TNM klassifiseringssystemet ble brukt for stadium-inndeling av pasientenes sykdom, og tumorrespons etter behandling ble evaluert etter RECIST 1.1. Overlevelse ble estimert ved bruk av Kaplan Meiers metode, og Cox proporsjonal hazard modell ble brukt for multivariabelanalyser, der det ble justert for pasientkarakteristika og sykdomskarakteristika.

Resultater

Vi identifiserte 226 pasienter behandlet med stereotaksi ved vår institusjon fra 2007 til 2019. Siste oppfølgingsdato ble satt til 30. juni 2020. Median alder var 74 år, og pasientgruppens Charlson Comorbidiy Index Score viste en median på 2 poeng. 23,9% oppnådde komplett respons, 36,3% oppnådde partiell respons mens 20,8% hadde stabil sykdom og 1,3% progredierte. Median total overlevelse var 40,7 måneder, og 1-års, 2-års og 5-års total overlevelse var henholdsvis 86%, 66% og 39%. 1-års og 5-års progresjonsfri overlevelse var 72% og 37%. Kun en marginal reduksjon i lungefunksjon ble funnet (-0,1 L i FEV1 og -0,4% i FEV1%) og få pasienter rapporterte bivirkninger; de vanligste var dyspné (4,4%), brystsmerter (3,1%), hudreaksjon (2,7%) og costafraktur (2,7%). Senere, fikk 12,4% lokalt residiv, 15,5% ble diagnostisert med ny primær tumor og 15,5% utviklet metastaser, vanligst i skjelett/muskel (5,8%), hjerne (5,3%) og lever (4,9%). 50,7% døde residivfri og 23,9% døde av sin lungekreft.

Konklusjon

Vår studie viser at stereotaksi ble godt tolerert, og sykdomskontroll og overlevelse etter behandling er lignende det som har blitt rapportert i internasjonale studier. Stereotaksi viser seg å være et trygt og effektivt behandlingsalternativ for medisinsk inoperable pasienter.

Introduction

Lung cancer is the second most common type of cancer in both men and women in Norway and makes up about 10% of all new cancers in Norway [2], with 1659 cases among men and 1661 cases among women in 2019 [1]. The five-year survival is low but rising, with 29% for women and 23% for men in 2019 [3], and it is the cancer type that takes the highest number of lives, with 1117 men and 1044 women dying of lung cancer in Norway in 2019 [1]. The reason behind this high mortality is that lung cancer is often detected late due to few and vague symptoms and has reached an advanced stage at time of diagnosis, leading to palliative treatment being the only available option for most patients [3, 5]. The median age is also 71 years for both sexes, which makes the patient group prone to a worse prognosis due to more comorbidity and because the majority have been smoking for a long time [3]. At the same time, for patients with early-stage disease who are candidates for curative treatment, the survival rate is much higher, with 5-year survival of 61.6% for men and 70.8% for women with localized (stage I) lung cancer in Norway 2019 [1].

Lung cancer is divided into two main groups: non-small cell lung cancer (NSCLC) affecting 85% of lung cancer patients, and small-cell lung cancer (SCLC) affecting 15% [1]. This project involves patients diagnosed with stage I NSCLC, who have received stereotactic body radiation therapy as a curative treatment.

Treatment of lung cancer

Surgery has traditionally been the most important curative treatment for stage I NSCLC and is preferred for patients who are medically and technically operable [2]. For inoperable patients, both conventional radiation therapy and stereotactic body radiation therapy (SBRT) are alternative curative treatments [1]. Curative fractionated radiation therapy used to be the only noninvasive alternative to surgery, but SBRT has proven to be more effective and is now considered the best therapy for inoperable patients [22]. SBRT provides higher local control rates and less toxicity compared to conventional radiotherapy [22]. In Norway, St. Olav's Hospital was the first institution to implement the use of stereotactic body radiation therapy for stage I NSCLC, and it has been offered to patients here since 2006. Later, SBRT has become available in all health care regions in Norway. Before the introduction of SBRT, the national guidelines recommended that 25% of the lung cancer patients should receive surgery. With the introduction of SBRT, the proportion who undergo surgery has remained stable, while the number of patients receiving curative treatment has increased and is now 37% [1].

Patients ineligible for curative treatment are offered palliative radiotherapy, chemotherapy or immunotherapy, to prolong survival time and improve quality of life [3].

What is SBRT?

Stereotactic body radiation therapy allows for delivery of ablative radiation doses to tumors in one to ten fractions, by delivering the radiation from various angles to converge on one target [6]. The dose distribution allows for a significant reduction of the dose within a few millimeters beyond the target, sparing nearby, crucial structures from radiation-induced damage. SBRT has quickly been adopted to clinical practice worldwide, and the obvious advantage of SBRT is the significantly better survival compared to conventional radiotherapy [22]. The superior survival is most likely due to delivery of precise, and high doses of radiation where the BED (biologically effective dose) in some SBRT dose-fractionation regimes reaches at least 100 Grey while the BED of conventional radiation therapy only reaches 80 Grey or less [22].

In addition, SBRT provides a reduced overall treatment time from several weeks for conventional radiotherapy to a few days, and thus requires less resources [10]. The main criteria for receiving SBRT is a tumor size < 6 cm, although exceptions can sometimes be made for peripheral tumors. For tumors located near large vessels or central airways a schedule with more fractions (often 5-11) with lower fraction dose is preferred to avoid perforation of vital structures [2]. Fractionation has been hypothesized to improve the therapeutic ratio as well, reducing the risk of late complications that potentially could be associated with a large single dose [4].

Why SBRT?

With a growing older population and an increasing use of CT-screening [10], a higher number of patients with NSCLC will now present at an early stage. Even though surgical resection remains the gold standard for management of patients with early-stage lung cancer, many patients are marginally operable or not operable due to severe pulmonary dysfunction or other comorbidities [8]. As an alternative, stereotactic body radiation therapy can now be offered to these patients.

SBRT has shown to provide excellent local control as well as minimal toxicity, and it has gradually replaced conventional radiotherapy (CRT) in treatment of inoperable stage I NSCLC [11, 32]. Several prospective trials have led to accumulating clinical experience with SBRT and have shown that SBRT provides with local control in about 90% and 3-year disease-specific survival in 72-88% of patients [18]. SBRT for lung cancer is now being provided in modern cancer centers worldwide [33, 34], and is recommended as the standard of care for medically inoperable patients who are eligible for curative treatment [34, 35, 36]. Regardless of age, the treatment causes little toxicity. According to the RTOG criteria (Toxicity criteria of the Radiation Therapy Oncology group), less than 10% experience grade 3 toxicity and the risk of severe long-term morbidity is below 3% [2]. Most common acute side-effects are cough, fatigue, dyspnea, pain, rib fracture etc. [19].

Due to the encouraging treatment results of SBRT, there has been an increasing interest in the oncology community about the comparative outcomes of SBRT and surgical resection [13]. Unfortunately, no prospective, randomized trials have been performed. Two independent, randomized, phase 3 trials of SBRT in patients with operable stage I NSCLC (STARS and ROSEL), closed early due to slow accrual [6]. A pooled analysis of data from these two trials, found a significantly higher OS for the SBRT group with a pooled estimate of 1-year and 3-year-OS of 100% and 95% in the SBRT group compared 88% and 79% in the surgical group [6].

As documented in several studies, there is a dramatic difference in pulmonary function, age, and comorbidity between the surgery group and SBRT group [8] with the latter group often being associated with worse prognostic factors [9]. This results in limitations in the studies comparing the outcomes of both treatment groups.

However, all evidence prove that lobectomy is superior to surgical resection [41, 42, 43], and considering that SBRT only targets the tumor, surgery should be more effective than SBRT and is still preferred if the patient's condition allow it.

SBRT at St. Olav's Hospital

Even though SBRT is now offered nationally, there is a significant difference between the percentage of patients receiving SBRT between the hospitals in Norway [1]. According to the national rapport from 2019, only 1.4% of lung cancer patients received SBRT in the Health Region of Central Norway, while corresponding numbers were 8.5% in South-East Norway and 6.8% in the Western region. The reason behind this number, is that a higher percentage at our institution receives surgery. Still, it is not known whether a higher proportion should receive SBRT at St. Olav's Hospital or why the distribution differs this much from the other health regions. In addition to these deviating numbers, a former PhD-project by our group (Trine Stokstad, "Timelines in lung cancer diagnostic workup") found shorter survival time and higher percentage of relapses and metastases among our SBRT-patients compared to what has been reported previously. The purpose of this study was to evaluate treatment outcomes of all patients undergoing SBRT at our hospital.

Methods

Patients

To find the patients included in this study, the patient administrative system of the radiotherapy section of St. Olav's Hospital was accessed and searched based on radiation fractionation. A list was retrieved including all patients that have received stereotactic body radiation therapy, also including date of treatment start, total radiation dose, and fractionation. We included all patients who were

radiated from January 2007 to December 2019. Some of the patients received multiple rounds of SBRT either for synchronous tumors or later relapse, and these were only registered once for their first round of receiving SBRT.

Data collection

Patient data was collected by reviewing the hospital charts. Baseline characteristics, data regarding pre-treatment investigations, fractionation regimes, toxicity, and further progression or remission was collected directly from the available journal both from St. Olav's Hospital and from institutions in the Health Region of Central Norway; more specifically the hospitals of Molde, Volda, Kristiansund, Ålesund, Levanger and Namsos. Data regarding tumor response were obtained from the radiologist's description of the CT scans taken after treatment. Some of the patients switched residency after treatment and continued further follow-up at a health institution outside of Central Norway, which therefore made some of the data inaccessible for us.

Assessments

To determine the degree of comorbidity, age adjusted Charlson's comorbidity score was used. The diagnose date was either the date of the pathology report, or when the CT scan or PET scan could confirm active disease for those who had neither histology nor cytology. In patients who had a lesion that was followed over a longer time the diagnose date was set to when the lesion progressed or new progressive lesions appeared, leading to the conclusion of active disease and an intervention being necessary.

The TNM classification 8th edition was used for TNM-staging of the tumor. The tumors were evaluated based on the revised RECIST guideline (version 1.1) [14]. The baseline measurements were collected from the last CT scan prior to treatment, usually performed within four weeks before treatment start. The longest diameter in one plane of the target lesion was recorded. For those who had multiple target lesions, this was recorded separately, but only the largest target lesion was included in the baseline sum of diameters and in further response evaluation after treatment. For the patients receiving treatment multiple times, only their first round of therapy and data regarding the radiated tumor was recorded and included in the analyses. Nodal lesions were not included in the baseline measurements or in follow-up evaluations, but instead the emergence of pathological nodes was registered as well as their disappearance. Follow-up CT scans were evaluated to record tumor response as either CR, PR, PD or SD based on the definitions from the RECIST guideline (version 1.1) which defines CR as disappearance of the target lesions and all pathological lymph nodes with a short axis under 10 millimeters, PR as at least a 30% reduction compared to the baseline measurement, PD as at least a 20% increase from the baseline measurement with at least an increase in 5 millimeters;

also including the patients with appearance of any new tumor suspected lesions, and SD was set when the criteria of PD or PR could not be reached, using the baseline measurement as a reference. Since this was a retrospective study, CT-scans were not taken systematically at specific time points after treatment, and therefore the best overall response was collected including the time until best response.

When evaluating disease progression, local relapse was defined as progression of a tumor or appearance of new tumors in the same lobe. New primary tumor was defined by progression of a lesion in a separate lobe without metastases to overlapping lymph nodes or multiple extra-thoracic metastases simultaneously, to distinguish from lung metastases. To determine the certainty of progression, a distinction was made between verified progression confirmed by biopsy or cytology, very high chance of progression defined by distant metastasis detected on MRI or CT scans, and high chance of progression defined by significant progression of the tumor only seen on CT scans.

Statistical methods

The descriptive analyses on baseline characteristics and the disease characteristics were performed using SPSS Statistics version 27. Overall survival was estimated using the Kaplan Meier method, and was calculated from end of treatment date to death date or last follow-up date, 30th of June 2020 (at which point all the patients still alive were censored). Progression free survival was calculated from end of treatment date to the event being any of the following: local recurrence, recurrence of new primary lung tumor, distant metastasis and otherwise death date or last follow-up date.
The Cox proportional hazard method was used for the multivariate analyses adjusting for baseline and disease characteristics, and hazard ratios (HR) with 95% confidence intervals (CI) was calculated. Statistical significance was defined as a p-value ≤ 0,05.

Results

Patient characteristics

We identified 226 patients at our institution treated with stereotactic radiation therapy from 2007 to 2019. Table 1 shows the baseline characteristics of the patients. The last follow-up date was June 30th, 2020. At the last follow-up date, 84 patients were still alive whereas 64 of them were still progression-free. Among all the patients, including the ones who were censored or died before last follow-up date, 136 patients had no relapse during their follow-up time.

The patient population consisted of 48.7% women and 51.3% men, and median age at radiation was 74 years. The group had severe comorbidity with a median CCI-score of 2.0 p (range 0-7 p) [Table 1]. A significant percentage of the patients had history of former cancer (39.4%), and 9.3%

of the patients had concurrent cancer at start of treatment [Table 2]. Most of the patient population had stage IA disease (73.0%), while 22.6% had stage IB, 3.1% had stage IIA and only 0.9% had stage IIB [Figure 2]. The median tumor size was 20.0 mm (range 6.0 – 52.0), and 10.2% had multiple synchronous tumors [Table 3]. Only 28.8% had biopsy-proven disease before treatment, and 1.3% of the patients had confirmed the diagnosis with cytology. The proportion with adenocarcinoma was slightly higher than squamous cell carcinoma (14.2% and 12.8%, respectively) [Table 3].

Table 1. Baseline patient characteristics.

		n = 226	**%**
Age at diagnosis	Median (range)	74 (43 – 92)	
Sex	Women	110	48.7%
	Men	116	51.3%
Smoking history	Never	18	8%
	Former	97	42.9%
	Current	100	44.2%
Charlson Comorbidity Index	Median (range)	2.00 points (0 – 7)	
Comorbidity	Lung disease	160	70.8%
	Heart disease	102	45.1%
	Vascular disease	70	31.0%
	COPD	150	66.4%
	Asthma	24	10.6%
FEV1	Median (range)	1.23 (0.44 – 3.74)	
FEV1 %	Median (range)	53.3% (26.2% - 94.5%)	

Figure 1. ECOG Performance Status.

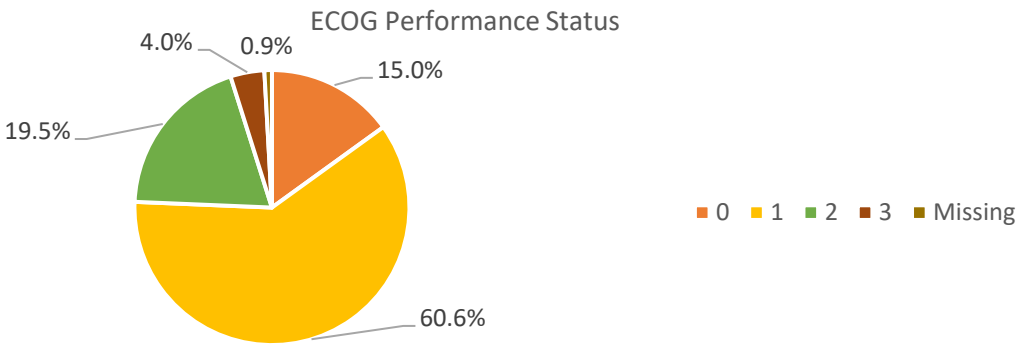


Table 2. Other cancer.

Former cancer	n	%	Synchronous cancer	n	%
Overall	89	39.4%	Overall	21	9.3%
Lung	50	22.1%	Prostate	6	2.7%
Bowel	12	5.3%	Bowel	4	1.7%
Prostate	8	3.5%	Gastric	2	0.9%
Breast	5	2.2%	Esophageal	1	0.4%
Ventricular	4	1.8%	Liver	1	0.4%
Rectal	3	1.3%	Laryngeal	1	0.4%
Skin	3	1.3%	Breast	1	0.4%
Lymphoma	3	1.3%	Oropharyngeal	1	0.4%
Lip	2	0.9%	Thyroid	1	0.4%
Bladder	2	0.9%	Bladder	1	0.4%
Laryngeal	2	0.9%	Follicular	1	0.4%
Endometrial	2	0.9%	Myeloma	1	0.4%
Oropharyngeal	1	0.4%			
Bone	1	0.4%			
Renal	1	0.4%			
Testicular	1	0.4%			
Thyroid	1	0.4%			

Figure 2. TNM-stage of disease

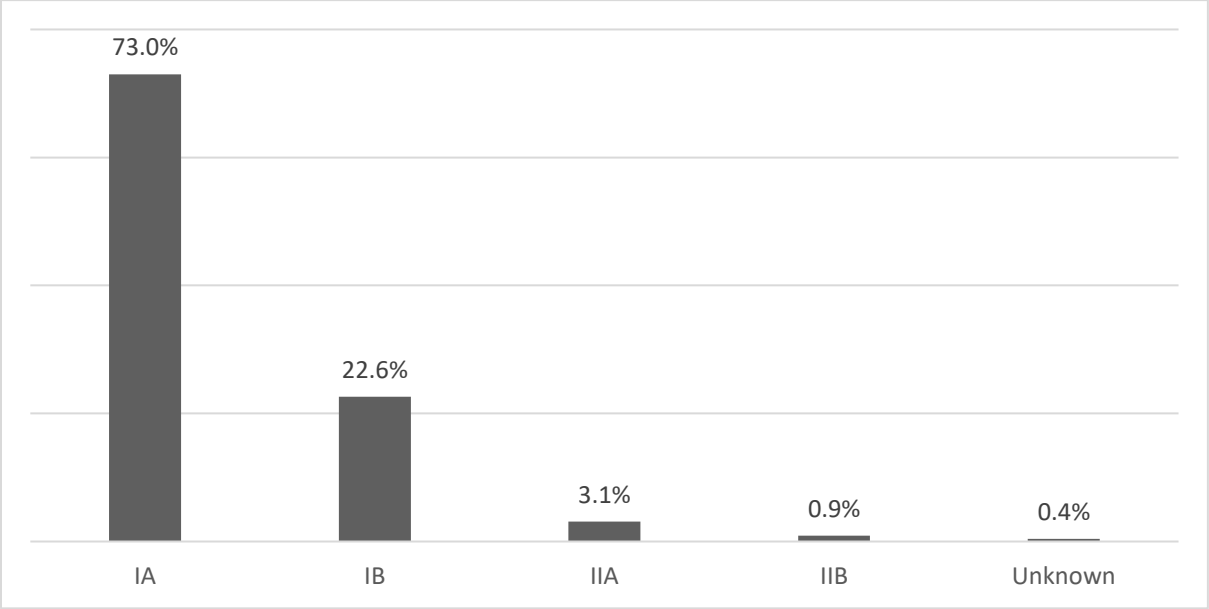


Table 3. Disease characteristics.

		n	%
Multiple synchronous tumors	Overall	23	10.2%
	In other lobe	21	9.3%
	Contralateral	15	6.6%
	Ipsilateral	5	2.2%
	Contralateral and ipsilateral	1	0.4%
	In one lobe	2	0.9%
Verified lung cancer	Histology	65	28.8%
	Cytology	3	1.3%
Histology	Adenocarcinoma	32	14.2%
	Squamous cell carcinoma	29	12.8%
	Other	9	3.9%
	Unknown	156	69.0%

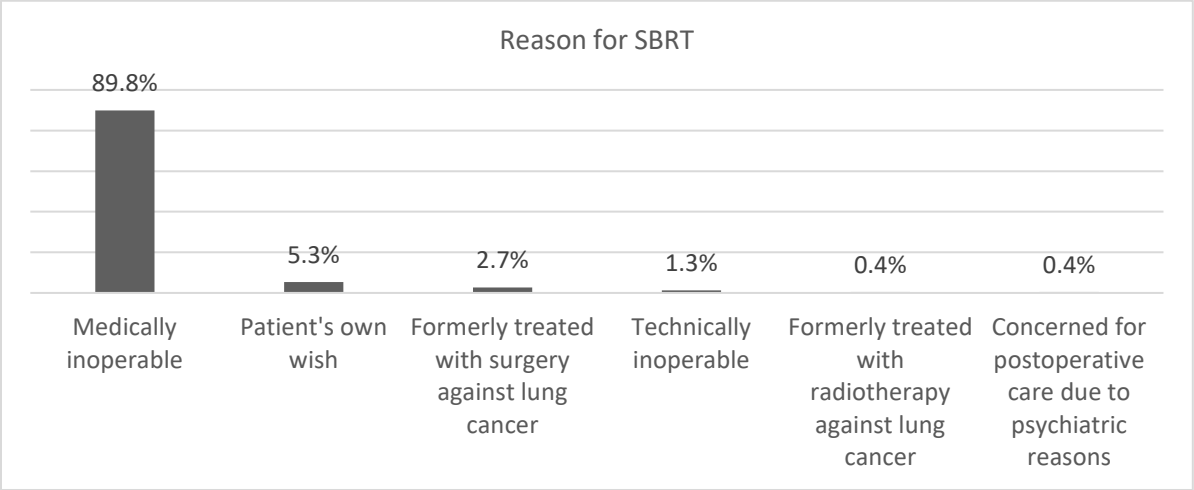
Pre-treatment investigations

Before October 2013, St. Olav's Hospital did not have a PET-scan, and we see that the proportion receiving a PET-scan increases from 54% in SBRT-patients before 2013, to 86.5% after 2013. Many of the patients were evaluated in an MDT-meeting to discuss if they were candidates for surgery beforehand, but for some of the patients this was not necessary before determining SBRT as their treatment strategy. The most common reason for receiving stereotactic body radiation therapy was medical inoperability applying to 89.8% of the patients, whereas 5.3% of the patients did not want surgery, 2.7% were formerly treated with lung cancer surgery and 1.3% had technically inoperable tumors [Figure 3].

Table 4. Pre-treatment investigations.

	n	%
PET	175	77.4%
MR caput	13	5.8%
Evaluation in MDT-meeting	157	69.5%

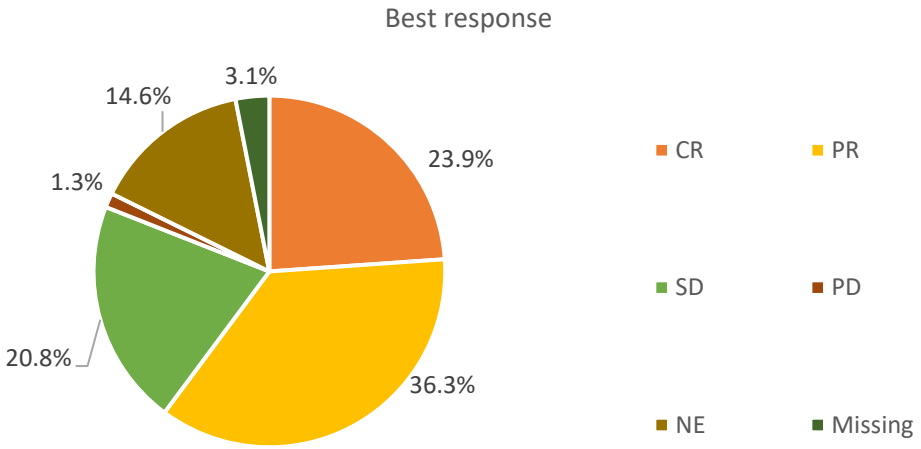
Figure 3. Reason for SBRT.



Response and post-treatment effects

Post-treatment, the overall response was 60.2%, while 20.8% had SD and 1.3% had PD [Figure 4]. A proportion of the patients were however non-evaluable, due to radiation sequela in the lung tissue preventing accurate measurement of the tumor size. Median time until PR was 4.0 months (range 1.3 – 25.4), and median time until CR was 10.3 months (range 2.8 – 32.9).

Figure 4. Best response (RECIST-criteria 1.1).



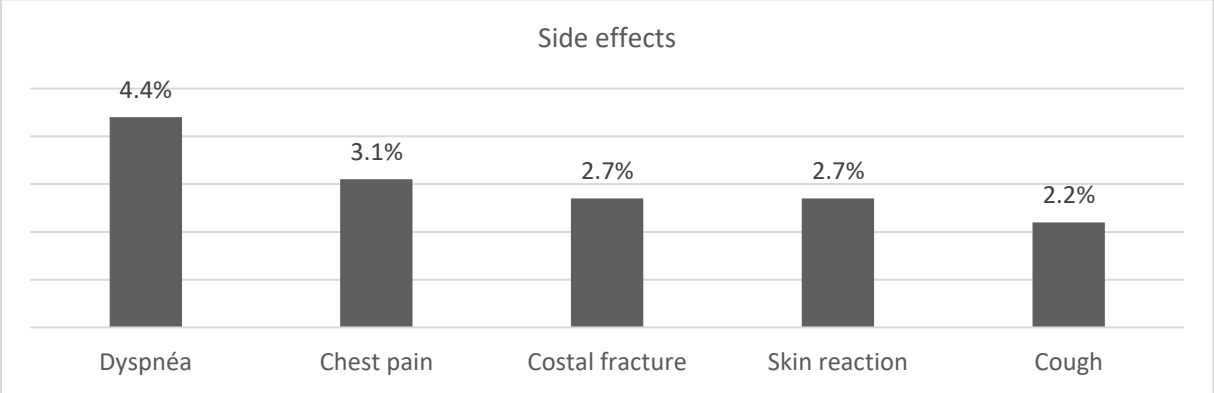
We found only a small reduction in lung function when evaluating spirometry examinations taken within a year after treatment [Table 5]. Only 15.5% of the patients had reported any side effects after therapy. The ones reported included dyspnea, chest pain, skin reaction, costal fracture and cough [Figure 5].

Table 5. Change in lung function after SBRT.

FEV1 after treatment[a]	Median (range)	1.1 (0.4 – 3.6)
FEV1% after treatment[a]	Median (range)	53.1% (26.0% - 90.0%)
Change in FEV1		- 0.1 L
Change in FEV1%		- 0.4%

[a] *Missing 124*

Figure 5. Side effects.



Relapse pattern

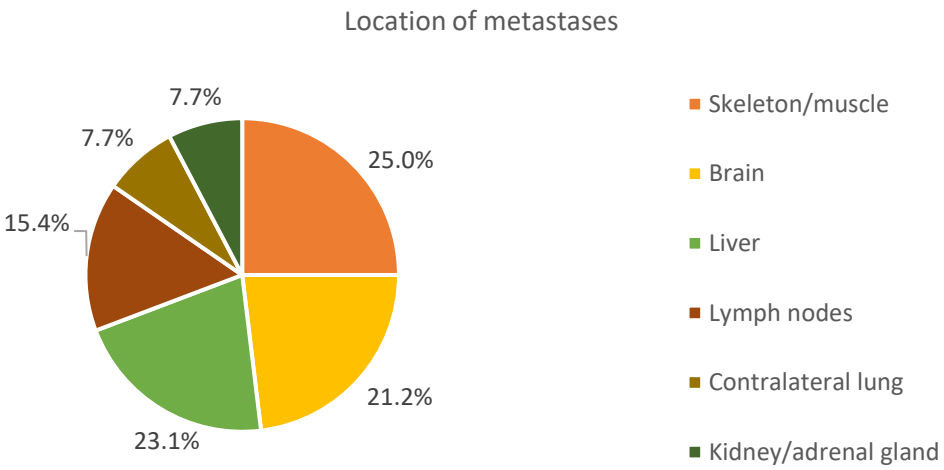
Local tumor control rate was 87.6%, whereas 12.4% were diagnosed with local relapse. Also, 15.5% were diagnosed with new primary lung tumor. The most common metastatic locations among the patients were skeleton/muscle (5.8%) and brain (5.3%), whereas 4.9% had metastasis to several locations simultaneously [Figure 6a]. The median time to progression, defined as either local relapse or metastatic disease was found to be 11.1 (3.0 – 44.8) months [Figure 6b].

Table 5. Relapses and metastases.

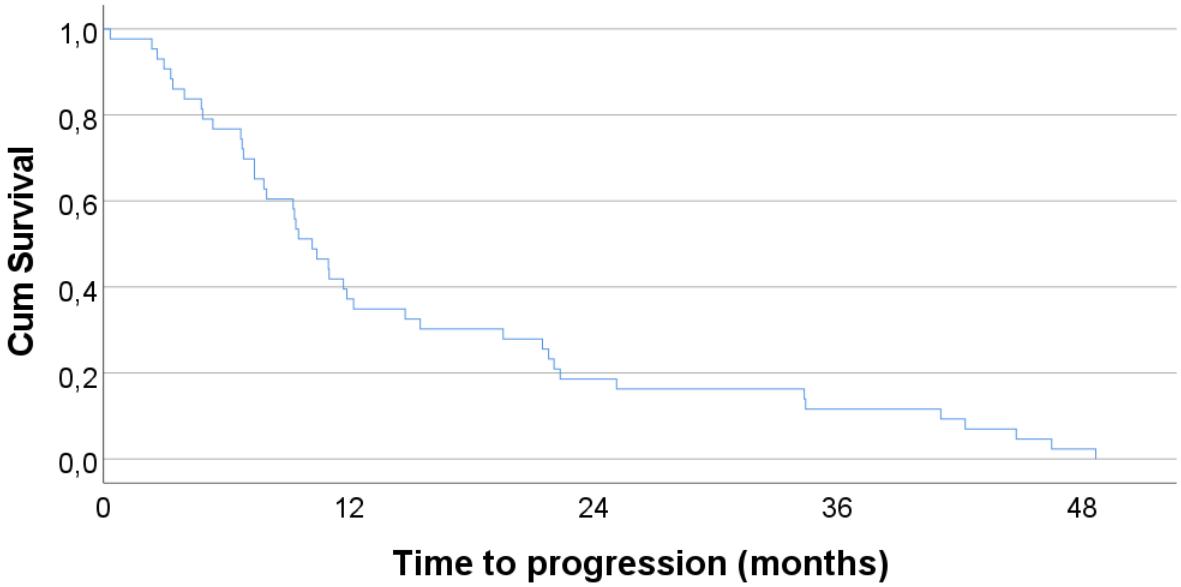
	n	**%**
Number with assumed local relapse	28	12.4%
Number of assumed new primary lung tumor	35	15.5%
Number with assumed new primary tumor and local relapse	6	2.7%
Number of assumed metastasis	35	15.5%
Number of assumed distant metastasis	28	12.4%
Number with assumed metastasis and local relapse	9	4.0%

Figure 6.

a) Location of metastases.



b) Time to progression.

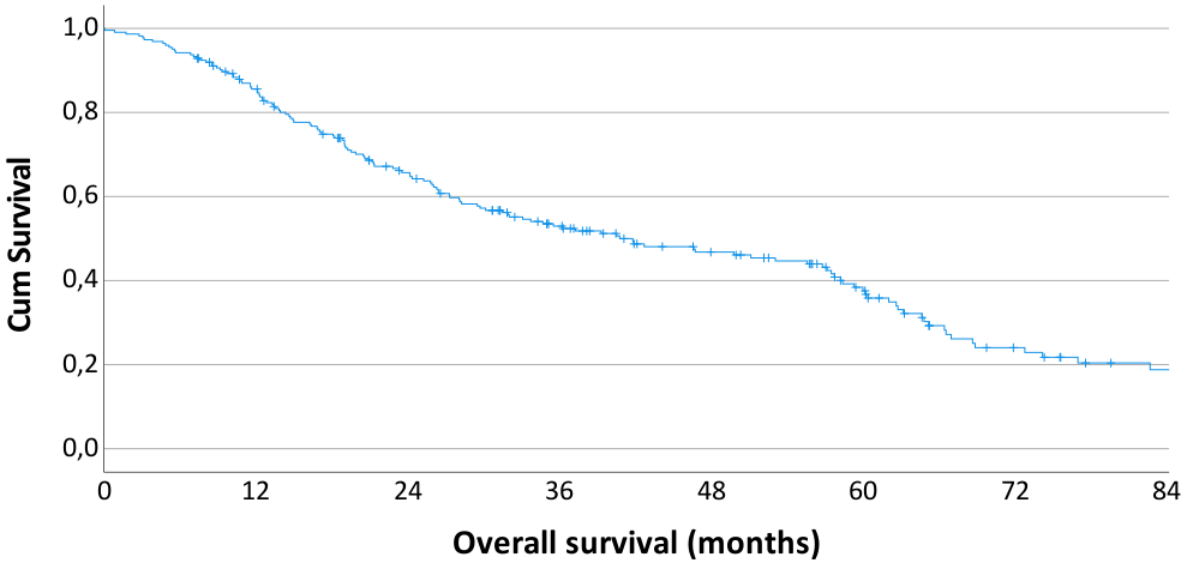


Survival

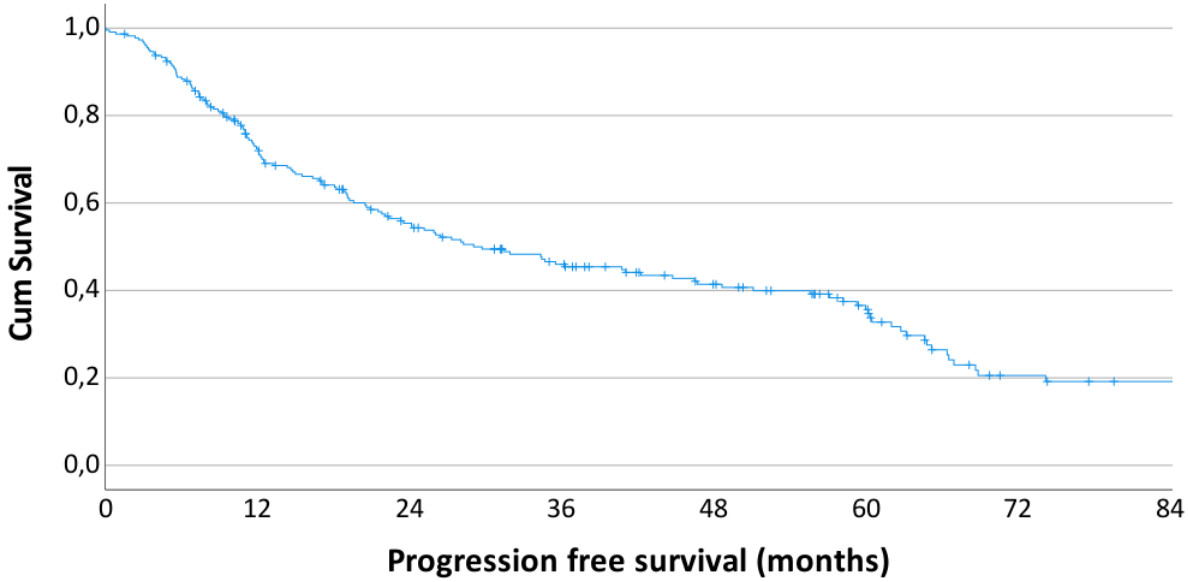
Finally, median overall survival was 40.7 months, and median progression free survival was 29.7 months [Figure 5a, b]. The 1-year, 2-year and 5-year OS was estimated to be 86%, 66% and 39%, and 1-year and 5-year progression free survival was 72% and 37%. More than half of the patients died relapse free (50.7%), and 23.9% died of their lung cancer. The cause of death was uncertain in approximately 14% of the patients, due to difficulty determining whether patients died from lung cancer or the comorbidities they simultaneously were suffering from [Figure 5c].

Figure 5. Survival and cause of death.

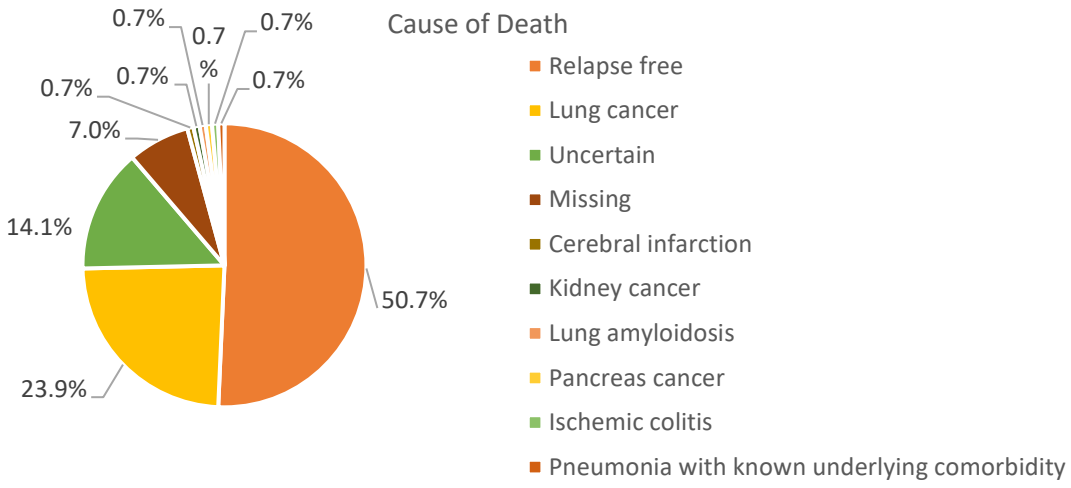
a) Overall survival.



b) Progression free survival.



c) Causes of death.



Discussion

In this retrospective study of patients treated with SBRT for lung cancer at St Olav's University Hospital from 2007 to 2019, we found an overall response of 60.2%, a median overall survival of 40.7 months, and 1-, year, 2-year and 5-year survival rates of 86%, 66% and 39 %, respectively. Median progression free survival was 29.7 months, and 1-year and 5-year progression free survival rates of 72% and 37%, respectively. Few reported side effects (15.5%) and 50.7% of patients died without relapse.

Compared to recently published meta-analyses and systematic reviews, others have found similar overall survival rates. Li et al. found a 1-year, 2-year and 5-year survival rates of 86.2%, 69.3% and 29.3% [22], and Zheng et al. found respectively 83.4%, 56.6% and 41.2% [15]. Another recent meta-analysis found survival rates of 86.9%, 58.8% and 41.3% respectively, similar to what we observed (86%, 66% and 39%) [31]. Median OS (28.0 – 38.4 months) is similar to what we observed of 40.7 months [22, 23, 24, 15, 31].

The progression free survival for our patients seems, however, to be lower than in other studies. A recent meta-analysis found a 1-year and 5-year PFS of 92.5% and 75.1%, which is higher than in our population (72% and 37%) [22]. On the other hand, Chi et al. found PFS-rates at 1-year and 5-year of 80.2% and 37.7% [31]. However, PFS is susceptible to evaluation intervals. Patients in our retrospective study did not undergo a systematic response evaluating, and the intervals between CT scans varied significantly. This might have influenced our PFS-data and might explain why they are inferior to other studies. Furthermore, it is often difficult to distinguish radiation sequela from tumor recurrence and very few relapses were verified with a biopsy or cytology.

There are a few factors that might have affected our survival outcomes. For instance, since few of our patients had biopsy-proven disease before treatment, nonmalignant lesions may have been included which may have led to overestimated survival. However, IJsseldijk et al. compared outcomes of biopsy-proven disease versus clinically diagnosed disease and found only a significantly lower 3-year overall survival in the biopsy-proven group, and no significant difference in 1-year, 2-year, or 5-year overall survival [23]. Since 89% of the SBRT-receiving patients were medically inoperable, survival may be determined by comorbidities rather than their assumed malignancy. Still Li et al. found survival outcomes similar to ours in their study of only inoperable patients [22].
The proportion metastasizing was also similar compared to larger studies [27, 28, 30 31], where we found a metastasis rate of 15.5% when including lymph node- and contralateral lung metastases, and extra-thoracic metastasis rate of 12.4% when disregarding the lymph node- and contralateral lung metastases. In an American retrospective study including 363 patients aiming to analyze patient and tumor factors and their association with the rate of metastases, found a rate of 17.2% with distant metastasis [27]. This study did consider limited contralateral lung parenchymal failures as local failure but did otherwise follow the distant site definitions of American Joint Committee on Cancer seventh edition staging. Another American study including 366 patients found a 2-year cumulative incidence of distant metastasis of 15.5%, where all sites were included except lymph nodes and the irradiated area of the lung parenchyma [28]. Schonewolf et al. included 186 patients and found that at 5 years, 27.7% had developed nodal metastases and 12% had developed extra-thoracic metastases [30]. Even though numbers regarding rate of metastases are lacking from larger meta-analyses and systematic reviews, larger retrospective studies like these show that our rate of metastases are quite similar if not somewhat lower compared to others. We must also consider that the patients included in our study that were irradiated the last years before end of follow-up, did have quite a short follow-up time after treatment and that this may affect our estimates to some degree.

Limitations of the study

There are several limitations that can be pointed out. First, this study only included patients from one institution, which makes it hard to generalize to other patient cohorts. Despite this fact, one must also consider that St. Olav's Hospital is the only university hospital in the region of Middle Norway, consisting of 697 000 citizens, and for a large part of the study period was the only department offering SBRT in our region. Later, the oncology department in Ålesund started treating these patients, and these patients are not included in our study.

Most of our patients lack histologic or cytological verification of their lung cancer, which can raise question about some of the patients' diagnosis. Still, we found that PET-scan was used in most of these incidences, whereas according to current guidelines, a lesion can be considered malign if it

measures > 8 mm in diameter and show growth on two consecutive PET-scans [40]. In some of the cases, treating physicians were unsure regarding the certainty of progression, and further investigation was not done due to the patients' significant comorbidity and low performance status. In these cases, only the lobar location of the tumor was used for separating local relapse from new primary tumor due to a lack of histologic verification. In addition, separating between secondary tumors and lung metastases can also be problematic; and in this study only the patients with simultaneous occurrence of overlapping lymph node metastasis and metastasis to other locations were categorized as having lung metastases, when missing exact verification.

There are also potential limitations regarding the radiology reports. Several radiologists have investigated the CT scans, and inter-rater variation might have influenced the response evaluations. The CT-scans were obtained at different time points at different scanners, and the scanning protocols have probably changed over time. Furthermore, most of the patients had CT-scan at 3, 6 and 12 months after treatment, but there was not uniform follow-up. That said, the main challenge is probably distinguishing between relapse and radiation fibrosis when assessing local recurrences. The diagnosis of metastases is easier.

One can speculate whether the fact that a lower percentage receiving SBRT at St. Olav's Hospital may followingly mean our patients are suffering from more comorbidity, lower performance status and poorer lung function compared to SBRT-patients elsewhere. This may contribute to falsely low overall survival estimates, caused by patients in a larger extent dying of other causes rather than lung cancer. However, the patient characteristics obtained in other SBRT-studies seem to resemble our findings: In an American retrospective study including 554 patients, 67.9% had performance status 0-1 and 68.5% had COPD [11]. A danish retrospective study found that 75% had performance status 0-1, and a mean FEV1 of 1.06 L [17], and in an American study, 52% of patients had performance status 0-1, a mean FEV1 of 1.23 and mean FEV1% of 53% [16]. One might therefore assume, that even though a smaller percentage at our institution receive SBRT, it does not necessarily mean our patients have a worse medical condition compared to the international SBRT-population.

Lastly, the data collected from patient journals contain a great deal of subjectivity due to altering treating physicians during one patient course and from patient to patient, compared to the uniform way of registering data in randomized controlled studies. For instance, few patients were found to have side effects, but we do not know if treating physicians have been consistent with recording or asking for these. Some information was also lacking in a considerable percentage of the patients, for instance spirometry values, follow-up CT scans and data regarding remission or progression due to further follow-up done in a different health region in Norway.

Strengths of the study

There are several strengths to the study as well; firstly, the patient data has been collected by going through every patient journal. The patients included are the ones registered in the patient administrative system of the radiotherapy department at our institution and that are registered as having received an SBRT-fractionation regime, which eliminates any selection bias. The study's aim is also a strength itself, due to its explorative purpose, therefore eliminating any confirmation bias. The study has not restricted its purpose to certain elements or areas but has simultaneously gathered comprehensive data on each patient including both patient characteristics, treatment characteristics, changes from baseline and further follow-up including remission or progression and cause of death. This may create a more complete picture and eliminate any bias that may come from targeting only one specific patient variable when collecting data.

Each CT scan taken has been used to collect data regarding tumor response, thus following the response development through separate time points, and gathering the best response in addition to time until best response. The use of RECIST-criteria eliminated much of the subjectivity that may arise when evaluating tumor response in a retrospective study. Similarly, the established criteria for defining local relapse, new primary tumor and metastasis enhances the consistency even though there is a lack of histological verification both in primary and secondary tumors. In addition, the study included patients from 2007 until 2019, which gives a comprehensive view over the outcomes from SBRT at our institution over time.

Our interpretation of our results

Our study shows promising results for SBRT, with satisfying overall response and survival outcomes resembling international findings, despite our smaller percentage of SBRT-receiving population. Thus, our concerns raised by the PhD-project of Trine Stokstad appear to be unfounded and probably due to inclusion of SBRT patients in a limited time period (2011-2013), and we have not found any reason to change our current treatment policy.

Considering that our SBRT patients are the most frail stage I patients, we believe that our treatment results are satisfying, and one might even speculate that some patients undergoing surgery would have achieved sufficient disease control by SBRT. However, our study was not designed to evaluate whether our selection criteria for surgery and SBRT are appropriate. Notably, we have collected similar data as in this study on patients undergoing surgery in the same time period and will perform a propensity matched comparison to try to answer this important question.

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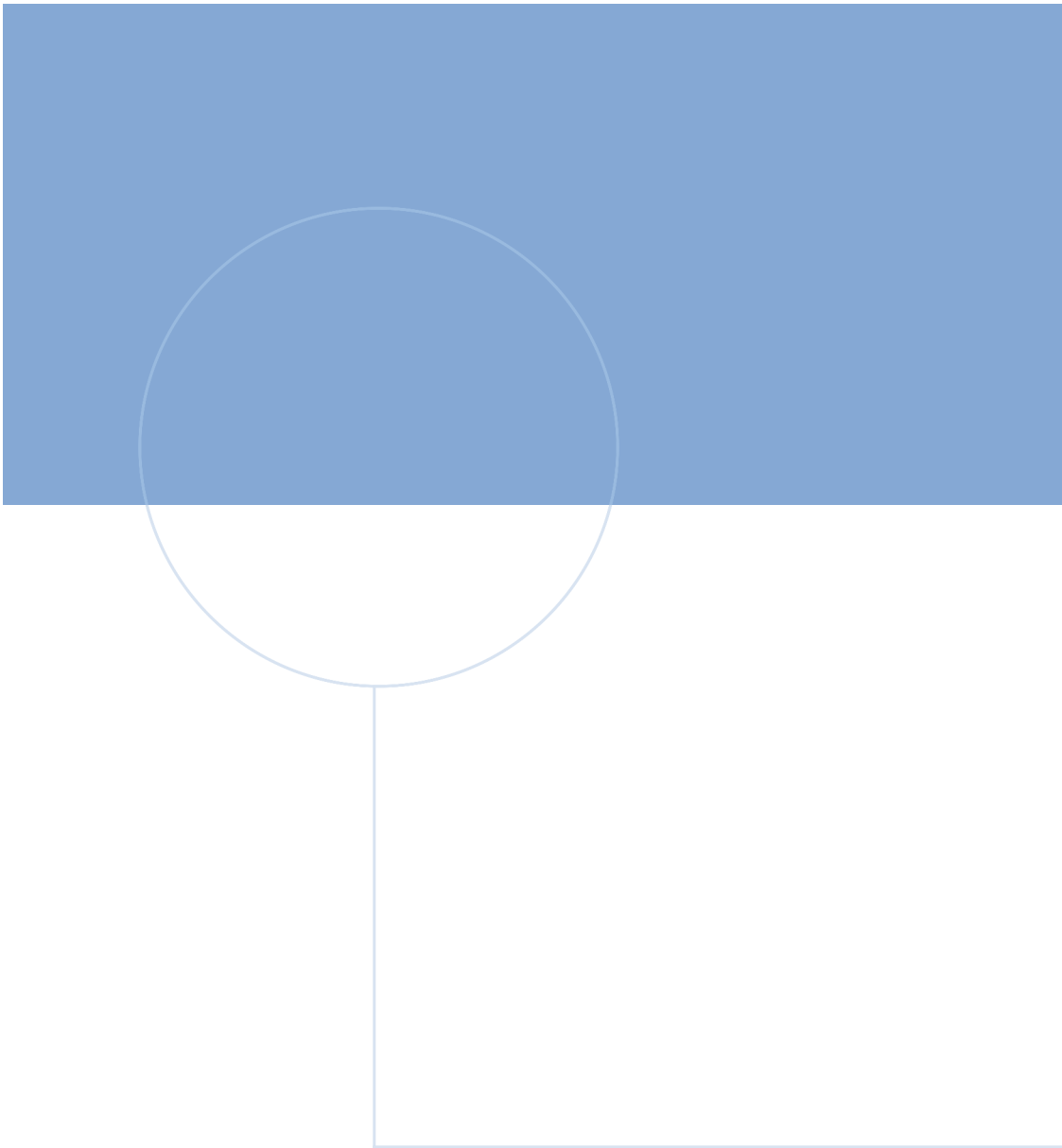

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