MENGFEI YUAN

"Observational Descriptive and Comparative Study of Patients Over 70 Years Old with Lung Cancer Oligometastasis Treated with a Radiotherapy Technique called SABR."

THESIS OF MASTER

Supervised by Dr. Meritxell Arenas Prat
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Máster en Envejecimiento y Salud

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"TRABAJO DE FIN DE MÁSTER"

Evaluación final

Tutor del estudiante: Dra. Meritxell Arenas Prat

Nombre del estudiante evaluado: MENGFEI YUAN

NOTA DE LA EVALUACIÓN FINAL **		
Pon la nota del 0 al 10 dentro de la casilla correspondiente		
	Ponderación	Nota 0 a 10
Evaluación global del trabajo 10%		
1. Claridad en la formulación de los objetivos y de los problemas		10
2. Coherencia interna del trabajo		10
3. El trabajo muestra el uso del pensamiento crítico		10
4. Relevancia: originalidad e innovación		10
5. Propuesta para la aplicación práctica de los resultados		10
Introducción y justificación 15%		
1. Explicación de las teorías que fundamentan el trabajo		10
2. Síntesis e integración de las teorías y del tema		10
3. Contribución en el avance teórico		10
4. Aportaciones a la sociedad y a la ética profesional		10
Metodología de la investigación 25%		
1. Adecuación de la metodología a la temática		10
2. Instrumentos de investigación apropiados		10
3. Descripción de los métodos utilizados		10
Resultados y discusión 20%		
1. Interpretación de los datos y resultados		10
2. Uso adecuado de los mecanismos de evaluación		10
3. Viabilidad de la propuesta		10
4. Uso adecuado de las herramientas de reflexión		10
5. Figuras y tablas adecuadas		10
Conclusión 20%		
1. Conclusiones relacionadas con los objetivos		10
2. Coherencia y adecuación de las conclusiones		10
Aspectos formales 5%		
1. Orden y claridad en la estructura del trabajo		10
2. Normativa (ortográfica, sintáctica, etc.) y corrección formal		10
3. Referencias bibliográficas actualizadas y formato adecuado		10
Evaluación del proceso 5%		
1. Ha mostrado capacidades de análisis, síntesis y razonamiento y se ve reflejado en el trabajo final		10
Nota total sobre 10: 10		

Consultar el documento "Criterios para puntuar las partes del TFM"

Observaciones (feedback): Yuan ha sido un alumno muy constante y muy trabajador. Misfelicitaciones por el gran TFM que ha realizado

Meritxell Arenas

Abstract

In the 2022 global cancer statistics data released, lung cancer has surpassed breast cancer to become the leading cancer worldwide, both in terms of incidence and mortality, accounting for approximately 18.7% of cases. Traditionally, most solid cancers in the metastatic status have been considered incurable. However, the concept of oligometastasis, an intermediate state between localized disease and widespread metastatic disease, has provided a new perspective for the treatment of metastatic lung cancer and other cancers. Stereotactic Ablative Radiotherapy (SABR) has emerged as a highly precise radiotherapy treatment. It is a non-invasive technique, as it does not require surgery nor an operating room and has a short treatment duration and effective radiation therapy procedure, considered a promising treatment option for oligometastatic lung cancer patients. Although SABR does not involve surgical incisions, some of the side effects it causes should not be overlooked, such as acute and chronic toxicity reactions. The objective is to investigate the clinical radiation response and toxicity in oligometastatic lung cancer elderly patients undergoing SABR in the Hospital Universitari Sant Joan de Reus. By analyzing the factors that might influence the outcomes and acute or late toxic reactions of SABR treatment, we did not find any significant differences. The results show that SABR is a good treatment option for older patients, demonstrating neither increased toxicity nor worse clinical responses. The treatment tolerance, response, and toxicity results are similar to those in the population under 70 years old.

Key words: elderly patient, Lung cancer, Stereotactic Ablative Radiotherapy (SABR), clinical outcomes, toxicity

Content

1. Introduction

Currently, cancer is a major cause of death, with an estimated 19.3 million new cancer cases worldwide and nearly 10 million cancer-related deaths in 2020. By 2040, it is projected that the global cancer burden will reach 28.4 million cases, representing a 47% increase from 2020 (1). The risk of cancer increases exponentially with age. Approximately 60% of cancers occur in individuals aged 65 or older. Additionally, 70% of cancer mortalities also occur in this age group (2). Research predicts that by 2050, there will be an estimated 6.9 million new cancer cases among adults aged 80 or older, accounting for 20.5% of all cancer cases (3). The most common types of cancer include lung, breast, prostate, and colorectal cancer. In 2022, lung cancer was the most commonly diagnosed cancer worldwide, resulting in nearly 2.5 million new cases and accounting for 12.4% of all global cancer cases (4). Lung cancer is also the leading cause of cancer-related deaths, with an estimated 1.8 million deaths. This is followed by colorectal cancer (9.3%), liver cancer (7.8%), female breast cancer (6.9%), and stomach cancer (6.8%). Additionally, lung cancer is the most common cancer among men, while breast cancer is the most common cancer among women(4). There are many factors contributing to lung cancer. Smoking is a key factor in the development of lung cancer. Among high-income populations, 9 out of 10 lung cancer cases are caused by smoking. Moreover, the mortality rate increases with the number of cigarettes smoked and the duration of smoking (5). Additionally, environmental exposure, chronic obstructive pulmonary disease, dietary metabolism, and genetic factors are also strongly associated with lung cancer (6) (7).

Metastasis means that cancer has spread to different parts of the body apart from where it started. The concept of oligometastasis, proposed by Hellman and Weichselbaum in 1995, is as an intermediate state between localized disease and widespread metastatic disease, characterized by early limited metastatic disease(8). Traditionally, most solid cancers in the metastatic status have been considered incurable. However, the concept of oligometastasis changed the paradigm and is considered a state with possibilities of treatment and cure. Since the introduction of this theory, research in this field has increased significantly (9). For example, relevant recommendations have been given for radical local treatment of different types of oligometastatic disease. Radiotherapy and surgery are the only major local treatment modalities recommended for patients with oligometastatic disease, and the indications for selecting these treatments are explained. Additionally, several recommendations have been provided for the optimal use of hypofractionated radiotherapy or SABR as definitive local treatment techniques, including dosage and fractionation (10).

Newly diagnosed metastases can be categorized into synchronous metastases and metachronous metastases. Synchronous metastases are diagnosed within six months of the diagnosis of the primary cancer, whereas metachronous metastases are diagnosed more than six months after the diagnosis of the primary cancer(11).

There are many methods for treating oligometastatic lung cancer, including surgery, radiation therapy, chemotherapy, immunotherapy, and targeted biologic therapy (12). Among them, radiation therapy is a commonly used and effective treatment method, which utilizes X-rays or other high-energy particles to kill cancer cells. Radiation therapy includes external beam radiation therapy and internal radiation therapy, is the first option(13). Different types of external beam radiation therapy include three-dimensional conformal radiation therapy (3DRT), intensity-modulated radiation therapy (IMRT), volumetric intensity-modulated arc therapy (VMAT), image-guided radiation therapy (IGRT), and Stereotactic Ablative Radiotherapy (SABR). SABR has emerged as a highly precise and effective radiation therapy procedure. It originated from the concept of stereotactic radiosurgery proposed by Lars Leksell in Sweden in 1951. It delivers high doses of radiation precisely to the tumor area, causing distortion or destruction of tumor cell DNA and damage blood vessels, leading to tumor cell reproductive failure and necrosis while sparing surrounding healthy tissue (14). Therefore, it is considered a promising treatment option. A randomized phase II trial conducted by Iyengar involved 29 non-small cell lung cancer patients with extracranial metastases before induction chemotherapy (including a median of 3 sites of disease), these patients were randomly assigned to receive maintenance systemic therapy alone or to receive SABR to all sites of disease in addition to maintenance systemic therapy. The results showed that SABR prolonged progression-free survival (PFS), with a median of 9.7 months in the SABR group compared to 3.5 months in the maintenance systemic therapy alone group (15).

SABR has several advantages, including its efficacy and precision in treating oligometastatic lung cancer. It is a non-invasive technique, as it does not require surgery nor an operating room and has a short treatment duration. In terms of its limitations, this technology is only suitable for sharply defined small cancers (target size less than 5 cm). For this reason, it is used in the early stages of cancer patients, who prefer or are unable to undergo surgery (16) (17) (18).

Although SABR does not involve surgical incisions, some of the side effects it causes should not be overlooked, such as acute and late toxicity reactions resulting from the treatment of lung cancer. Acute toxicity reactions include difficulty breathing, chest pain, radiation pneumonitis, dermatitis, esophagitis, myositis, and so on. Late toxicity reactions include radiation pneumonitis, difficulty breathing, coughing, chronic chest pain, chronic myositis, hypoxia, fatigue, lung collapse, asymptomatic radiation fibrosis, and others (19). Considering the special characteristics of elderly patients, who often have other chronic diseases and take multiple medications, greater toxicity reactions may occur months after SABR treatment, including both acute and chronic toxicity. This information can help doctors adjust treatment plans based on individual patient circumstances, including radiation dose, number of treatments, and choice of treatment area, to maximize treatment effectiveness and minimize adverse reactions, thereby improving patient’s quality of life (20).

2. Hypothesis and objectives.

The hypothesis of this study is that oligometastatic lung cancer elderly patients who undergo SABR treatment have favorable outcomes, but their treatment response and toxicity could be different compared to younger patients.

The primary objective is to investigate the clinical efficacy and radiation response in elderly patients undergoing SABR for oligometastatic lung cancer treatment.

The secondary objectives are the following:

1. To observe acute and chronic toxicity reactions in the body of elderly patients aged 70 and above after undergoing SABR for oligometastatic lung cancer.
2. To analyze the correlation between age and treatment response.
3. To explore other factors that may affect treatment response and toxicity in elderly patients with oligometastatic lung cancer, such as underlying diseases or toxic habits.

3. Methodology

3.1. Study Design

This is an observational, comparative study on the effectiveness of SABR in oligometastatic lung cancer patients aged 70 and above compared to those under 70 years old. All patients participating in the study were treated at the Oncology Radiotherapy Department of Hospital Universitari Sant Joan de Reus between May 2012 and December 2021. Follow-up was conducted by reviewing medical records, imaging data, and via telephone.

3.2. Inclusion and Exclusion Criteria

Inclusion Criteria

- Histological confirmation of primary lung cancer.
- Age ⩾ 18 years.
- ⩽ 5 metastases detected by imaging.
- Informed about the process of SABR treatment.
- Eastern Cooperative Oncology Group (ECOG) scale score 0-1.

Exclusion Criteria

- History of another cancer.
- Connective tissue disease.
- Pregnancy and/or breastfeeding.
- Inability to follow-up.

3.3. Variables to be Studied.

The main variable of this study is the treatment response according to RECIST criteria (21) of patients after receiving SABR (complete response, partial response, stable disease, or progression). The secondary variables include anthropometrics, comorbidities, toxic habits and acute and chronic toxic reactions related to SABR treatment.

3.4. Adverse Effects

No adverse effects have been considered as this is an observational study without direct intervention in the study population.

3.5. Ethical Approval

This study has been approved by the Ethics Committee of the Hospital Universitari

Sant Joan de Reus (Ref. 005/2023). All patients were informed and signed the consent form for the collection of their medical records.

3.6. Data Collection and Analysis

Statistical analysis was performed using SPSS 19.0 software.

Quantitative included BMI. Qualitative variables included gender, age group, smoking, alcohol consumption, hypertension, hyperlipidemia, pulmonary disease, cardiovascular disease, lung cancer histology, oncological family history, synchronous metastasis diagnosis, location of metastasis and number of metastasis.

The Shapiro-Wilk test was used to assess the normality of quantitative variables. The results showed that BMI followed a normal distribution ($P=0.46$). Therefore, BMI was described using mean and standard deviation ($x \pm s$).

For quantitative variable BMI that met the normality assumption, were analyzed using the two independent sample t-test. Qualitative variables were described using frequencies (percentages) and the chi-square test (χ^2) or fisher exact test was used to analyze influencing factors, with a significance level set at $\alpha=0.05$, considering $P<0.05$ as statistically significant.

4. Results

4.1. General Demographic Characteristics

This study included 65 oligometastatic lung cancer patients. We divided them into two groups based on age: the group aged over 70 with 35 people, and the group aged under 70 with 30 people. Both groups had similar proportions of males and females, indicating no significant gender difference between the groups, the average BMI was similar between both groups. Approximately 70% of patients in both groups had a history of smoking, indicating a high prevalence of smoking history among the study participants. Around 30% of patients in both groups had a history of alcoholism, showing a similar pattern of alcohol consumption. The proportion of patients having comorbidities such as diabetes, and hyperlipidemia was similar in both groups. However, patients with more than 70 years old showed a higher prevalence of hypertension. Patients having previous neoplasms, oncological family history or conditions like non oncologic pulmonary or cardiovascular diseases were present in both groups without significant differences. The proportions of patients regarding lung cancer histology, metastasis location, synchronous metastasis diagnosis, and number of metastases are similar between the two groups.

Table 1. Basic Demographic Characteristics of the Study Population

	<70	**≥70**	**p**
n	30	35	
Males	22 (73.3)	28 (80.0)	0.733
Alcoholism	11 (36.7)	9 (25.7)	0.494
Smoking	24 (80.0)	25 (71.4)	0.609
BMI	25.09±4.01	25.34±3.01	0.082
Diabetes	5 (16.7)	13 (37.1)	0.118
Hypertension	14 (46.7)	27 (77.1)	**0.023**
Hyperlipidemia	11 (36.7)	22 (62.9)	0.063
Pulmonary diseases			0.235
Bronchitis	0 (0.0)	1 (2.9)	
COPD	16 (53.3)	24 (68.6)	
Not	14 (46.7)	10 (28.6)	
Cardiovascular disease			0.459
CVA	1 (3.3)	1 (2.9)	

AF	0 (0.0)	3 (8.6)	
AMI	2 (6.7)	5 (14.3)	
CHF	3 (10.0)	5 (14.3)	
Not	21 (70.0)	18 (51.4)	
Others	3 (10.0)	3 (8.6)	
Previous neoplasm			0.249
Not	17 (56.7)	19 (54.3)	
Colorectal	2 (6.7)	4 (11.4)	
Gyne	1 (3.3)	0 (0.0)	
Breast	0 (0.0)	1 (2.9)	
Skin	0 (0.0)	2 (5.7)	
Prostate	1 (3.3)	0 (0.0)	
Lung	0 (0.0)	3 (8.6)	
Others	9 (30.0)	6 (17.1)	
Oncological family history	4 (13.3)	4 (11.4)	1
Lung cancer histology			1
NSCLC	29 (96.67)	33 (94.29)	
SCLC	1 (3.33)	2 (5.71)	
Synchronous metastasis diagnosis	9 (30.0)	14 (40.0)	0.562
Location of metastasis			0.080
Lung	19 (63.34)	30 (85.71)	
Head	1 (3.33)	0 (0.00)	
Bone	9 (30.00)	5 (14.29)	
Others	1 (3.33)	0 (0.00)	
Number of metastasis			0.108
1	19 (63.3)	30 (85.7)	
2	8 (26.7)	4 (11.4)	
3	3 (10.0)	1 (2.9)	

Abbreviations: Cerebrovascular Accident (CVA), Atrial Fibrillation (AF), Acute Myocardial Infarction (AMF), Body Mass Index (BMI), Bronchitis (BC), Chronic Heart Failure (CHF), Chronic obstructive pulmonary disease (COPD), Non-Small Cell Lung Cancer (NSCLC), Small Cell Lung Cancer (SCLC)

Categorical variables (%): the chi-square test (χ^2) or Fisher's exact test

BMI: Two independent sample t-test

4.2. Analysis of the impact of age on treatment outcomes and acute/chronic toxicity reactions

42.86% of patients with more than 70 years old achieved either complete or partial response to the treatment, and only 26.67% of patients younger than 70 years old achieved complete or partial response to the treatment. However, there were no statistically significant differences between groups. Regarding acute toxicity reactions, 23 patients with more than 70 years old experienced acute toxicity and 26 experienced chronic toxicity, accounting for 65.71% and 74.29% of the group. Among those with acute toxicity, only 4 cases exhibited grade 2 toxicity, and no case of grade 2 chronic toxicity. In patients younger than 70 years old, 15 patients experienced acute toxicity and 7 experienced chronic toxicity, representing 50% and 23.33% of the group. Among those with acute toxicity, only one case exhibited grade 2 toxicity, and there were no cases of grade 2 chronic toxicity. No significant differences were founded in acute and chronic toxicity between two groups.

Table 2. The impact of age on treatment outcomes and acute/chronic toxicity reactions

	＜70	**≥70**	**p**
n	30	35	
Treatment outcome			0.17
Complete or partial response	8 (26.67)	15 (42.86)	
Stable response or progression	22 (73.33)	20 (57.14)	
Acute Toxicity Reactions			0.20
Yes	15 (50.00)	23 (65.71)	
Chronic Toxicity Reactions			0.82
Yes	7（23.33）	26（74.29）	

Since there were no significant differences among young and old patients' outcome and acute and chronic toxicity, the effect of other clinical factors aside from age were analyzed. The results showed no statistically significant associations between the clinical factors studied and the response to treatment.

Table 3. Analysis of the Impact of Different Factors on Treatment Outcomes in the Elderly Group Aged ≥70

	Treatment outcome		
	Complete or partial response	**Stable response or progression**	**p**
n	15	20	
Males	12 (80.00)	16 (80.00)	1.00
Alcoholism	4 (26.67)	5 (25.00)	1.00
Smoking	11 (73.33)	14 (70.00)	1.00
BMI	25.77±2.49	25.02±3.73	0.28
Diabetes	5 (33.33)	8 (40.00)	0.74
Hypertension	13 (86.67)	14 (70:00)	0.42
Hyperlipidemia	10 (66.67)	12 (60.00)	0.74
Pulmonary diseases (COPD or BC)	11 (73.33)	14 (70.00)	1.00
Cardiovascular disease (CVA/AF/AMI/CHF/Others)	8 (53.33)	9 (45.00)	0.74
Oncological family history	3 (20.00)	1 (5.00)	0.29
Lung cancer histology			
NSCLC	7 (46.67)	11 (55.00)	0.74
SCLC	8 (53.33)	9 (45.00)	
Location of metastasis			0.37
Lung	14 (93.33)	16 (80.00)	
Bone	1 (6.67)	4 (20.00)	
Synchronous metastasis diagnosis	7 (46.67)	7 (35.00)	0.51
Numbers of metastasis			
1	14 (93.33)	16 (80.00)	0.77
2	1 (6.67)	3 (15.00)	
3	0 (0.00)	1 (5.00)	

Abbreviations: Body Mass Index (BMI), Bronchitis (BC), Chronic obstructive pulmonary disease (COPD), Non-Small Cell Lung Cancer (NSCLC), Small Cell Lung Cancer (SCLC)

Categorical variables (%): the chi-square test (χ^2) or Fisher's exact test

BMI: Two independent sample t-test

The same analysis was done to study the clinical factors that could be related to acute toxicity reactions to SABR treatment. The results showed there are no statistically significant associations between the acute toxicity reactions and the clinical factors studied.

Table 4. Analysis of the Impact of Different Factors on Acute Toxicity Reactions in the Elderly Group Aged ≥70

	Acute Toxicity Reactions		
	Yes	**No**	p
n	12	23	
Males	10 (83.33)	18 (78.26)	1.00
Alcoholism	2 (16.67)	7 (30.43)	0.45
Smoking	6 (50.00)	19 (82.61)	0.06
BMI	25.35±3.31	25.34±2.92	0.76
Diabetes	4 (33.33)	9 (39.13)	1.00
Hypertension	9 (75.00)	18 (78.26)	1.00
Hyperlipidemia	6 (50.00)	16 (69.57)	0.29
Pulmonary Disease (COPD or BC)	9 (75.00)	16 (69.57)	1.00
Cardiovascular disease	5 (41.67)	12 (52.17)	0.73
Previous neoplasm			
Not	6 (50.00)	13 (56.52)	0.74
Yes	6 (50.00)	10 (43.48)	
Oncological family history	0 (0.00)	4 (17.39)	0.28
Lung cancer histology			
NSCLC	5 (41.67)	13 (56.52)	0.49
SCLC	7 (58.33)	10 (43.48)	
Location of metastasis			0.64
Lung	19 (82.61)	11 (91.67)	
Bone	4 (17.39)	1 (8.33)	
Synchronous metastasis diagnosis	3 (25.00)	11 (47.83)	
Numbers of metastasis			0.74
1	20 (86.96)	10 (83.33)	
2	2 (8.70)	2 (16.67)	
3	1 (4.35)	0 (0.00)	

Abbreviations: Body Mass Index (BMI), Bronchitis (BC), Chronic obstructive pulmonary disease (COPD), Non-Small Cell Lung Cancer (NSCLC), Small Cell Lung Cancer (SCLC)

Categorical variables (%): the chi-square test (χ^2) or Fisher's exact test

BMI: Two independent sample t-test

the results represented in table 5 showed no statistically significant associations between the late toxicity reactions and the clinical factors studied.

Table 5. Analysis of the Impact of Different Factors on Chronic Toxicity Reactions in the Elderly Group Aged≥70.

	Late Toxicity Reactions		
	Yes	**No**	**p**
n	26	9	
Males	22 (84.62)	6 (66.67)	0.34
Alcoholism	7 (26.92)	2 (22.22)	1.00
Smoking	18 (69.23)	7 (77.78)	1.00
BMI	25.53±3.28	24.78±2.10	0.08
Diabetes	9 (34.62)	4 (44.44)	0.70
Hypertension	22 (84.62)	5 (55.56)	0.16
Hyperlipidemia	16 (61.54)	6 (66.67)	1.00
Pulmonary disease (COPD or BC)	17 (65.38)	8 (88.89)	0.24
Cardiovascular disease	11 (42.31)	6 (66.67)	0.26
Previous neoplasm			
Not	15 (57.69)	4 (44.44)	0.70
Yes	11 (42.31)	5 (55.56)	
Oncological family history	4 (15.38)	0 (0.00)	0.55
Lung cancer histology			
NSCLC	13 (50.00)	5 (55.56)	1.00
SCLC	13 (50.00)	4 (44.44)	
Location of metastasis			1.00
Lung	8 (88.89)	22 (84.62)	
Bone	1 (11.11)	4 (15.38)	
Synchronous metastasis diagnosis	11 (42.31)	3 (33.33)	0.71
Numbers of metastasis			1.00
1	8 (88.89)	22 (84.62)	
2	1 (11.11)	3 (11.54)	
3	0 (0.00)	1 (3.84)	

Abbreviations: Body Mass Index (BMI), Bronchitis (BC), Chronic obstructive pulmonary disease (COPD), Non-Small Cell Lung

Cancer (NSCLC), Small Cell Lung Cancer (SCLC)

Categorical variables (%): the chi-square test (χ^2) or Fisher's exact test

BMI: Two independent sample t-test

Due to the small sample size in the group aged over 70, and to reduce the systematic bias that may be caused by insufficient sample size, we analyzed and compared all possible influencing factors between the two groups.

Analysis of Factors Influencing Treatment Results

The statistical analysis of lung cancer subtypes shows a significant difference (p=0.04) in treatment response between NSCLC and SCLC. However, we observed that the majority of cases were concentrated in NSCLC, with 62 cases, while there were only 3 cases of SCLC. Since there were no cases of stable disease or disease progression in the SCLC group, the difference in data distribution limits the meaningfulness of this statistical difference.

Table 6. Univariate Analysis of Factors Influencing Treatment Results

	Treatment outcome		
	Complete or partial response 23	**Stable response or progression** 42	**p**
Gender	17 (73.91)	33 (78.57)	0.67
Alcoholism	6 (26.09)	14 (33.33)	0.55
Smoking	17 (73.91)	32 (76.19)	0.84
BMI	25.51±3.93	25.07±3.26	0.84
Diabetes	6 (26.09)	12 (28.57)	0.84
Hypertension	17 (73.91)	24 (66.67)	0.18
Hyperlipidemia	12 (52.17)	21 (50.00)	0.89
Pulmonary diseases (COPD or BC)	15 (65.22)	26 (61.90)	0.79
Cardiovascular disease	9 (39.13)	16 (38.10)	0.94
Oncological family history	5 (21.74)	3 (7.14)	0.09
Lung cancer histology			
NSCLC	20 (86.96)	42 (100.00)	**0.04**
SCLC	3 (13.04)	0 (0.00)	
Location of metastasis			0.33

Lung	19 (82.61)	30 (71.43)	
Synchronous metastasis diagnosis	8 (34.78)	15 (35.71)	0.94
Number of metastasis			
1	19 (82.61)	30 (71.43)	0.46
2	4 (17.39)	8 (19.05)	
3	0 (0.00)	4 (9.52)	

Abbreviations: Body Mass Index (BMI), Bronchitis (BC), Chronic obstructive pulmonary disease (COPD), Non-Small Cell Lung Cancer (NSCLC), Small Cell Lung Cancer (SCLC)

Categorical variables (%): the chi-square test (χ^2) or Fisher's exact test

BMI: Two independent sample t-test

Analysis of Factors Influencing Acute Toxicity Reactions

After analyzing factors which may influence acute toxicity reactions the results showed no statistically significant associations.

Table 7. Univariate Analysis of Factors Influencing Acute Toxicity Reactions

	Acute Toxicity Reactions		
	Yes	**Not**	**p**
n	38	27	
Males	30 (78.95)	20 (74.07)	0.65
Alcoholism	12 (31.58)	8 (29.63)	0.87
Smoking	31 (81.58)	18 (66.67)	1.70
BMI	24.78±3.47	25.54±3.51	0.65
Diabetes	12 (31.58)	6 (22.22)	0.41
Hypertension	26 (68.42)	15 (55.56)	0.29
Hyperlipidemia	20 (52.63)	13 (48.15)	0.72
Pulmonary Disease (COPD or BC)	25 (65.79)	16 (59.26)	0.59
Cardiovascular disease	15 (39.47)	10 (37.04)	0.84
Previous neoplasm			
Not	21(55.26)	15(55.56)	0.98
Yes	17(44.74)	12(44.44)	
Family history	6 (15.79)	2 (7.41)	0.31
Lung cancer histology			0.44
NSCLC	36 (94.74)	26 (96.30)	
SCLC	2 (5.26)	1 (3.70)	

Location of metastasis			0.44
Lung	30 (78.95)	19 (70.38)	
Bone	8 (21.05)	6 (22.22)	
Synchronous metastasis diagnosis	14 (36.84)	9 (33.33)	0.77
Numbers of metastasis			
1	31 (81.58)	18 (66.67)	0.29
2	6 (15.79)	6 (22.22)	
3	1 (2.63)	3 (11.11)	

Abbreviations: Body Mass Index (BMI), Bronchitis (BC), Chronic obstructive pulmonary disease (COPD), Non-Small Cell Lung Cancer (NSCLC), Small Cell Lung Cancer (SCLC)

Categorical variables (%): the chi-square test (χ^2) or Fisher's exact test

BMI: Two independent sample t-test

Analysis of Factors Influencing Late Toxicity Reactions

After analyzing factors which may influence late toxicity reactions, no one of the clinical factors studied showed significant associations.

Table 8. Univariate Analysis of Factors Influencing Chronic Toxicity Reactions

	Late Toxicity Reactions		
	Yes	**Not**	**p**
n	16	49	
Males	12 (75.00)	38 (77.55)	0.83
Alcoholism	5 (31.25)	15 (30.61)	0.96
Smoking	13 (81.25)	36 (73.47)	0.53
BMI	25.98±2.53	24.98±3.73	0.10
Diabetes	7 (43.75)	11 (22.45)	0.10
Hypertension	9 (56.25)	32 (65.31)	0.52
Hyperlipidemia	11 (68.75)	22 (44.90)	0.10
Pulmonary disease (COPD or BC)	12 (75.00)	29 (59.18)	0.26
Cardiovascular disease	9 (56.25)	16 (32.65)	0.09
Previous neoplasm			
Not	8(50.00)	28 (57.14)	0.62
Yes	8 (50.00)	21 (42.86)	
Oncological family history	0 (0.00)	8 (16.33)	0.09

Lung cancer histology			0.66
NSCLC	16 (100.00)	46 (93.88)	
SCLC	0 (0.00)	3 (6.12)	
Location of metastasis			0.29
Lung	13 (81.25)	36 (73.47)	
Bone	2 (12.50)	12 (24.49)	
Synchronous metastasis diagnosis	5 (31.25)	18 (36.73)	0.69
Numbers of metastasis			
1	12 (75.00)	37 (75.51)	1.00
2	3 (18.75)	9 (18.37)	
3	1 (6.25)	3 (6.12)	

Abbreviations: Body Mass Index (BMI), Bronchitis (BC), Chronic obstructive pulmonary disease (COPD), Non-Small Cell Lung Cancer (NSCLC), Small Cell Lung Cancer (SCLC)

Categorical variables (%): the chi-square test (χ^2) or Fisher's exact test

BMI: Two independent sample t-test

5. Discussion

This study observed the treatment outcomes and the acute and late toxicity reactions of SABR in elderly oligometastatic lung cancer patients aged 70 and above. After analyzing the difference of all influencing factors, this study demonstrated that the SABR in elderly patients with oligometastatic lung cancer was well tolerated, no difference in treatment response and toxicity radiotherapy treatment techniques in these patients, so this treatment will be a good option in this subgroup patients.

Smoking is recognized as one of the key factors contributing to lung cancer (4) (22). However, there is still relatively little clinical research on whether it affects treatment outcomes and acute/chronic toxicity during treatment. Condoluci et al suggests that continued smoking after lung cancer diagnosis is highly associated with poor prognosis, reduced survival rates, increased risk of second primary malignancies, and heightened risk of cancer recurrence (23). Whether smoke or how long time of smoking history before an SCLC diagnosis are not significant predictors of survival. However, patients who quit smoking at the time of diagnosis had a 45% lower risk of death compared to those who continued smoking. Additionally, they also achieved better quality of life (24). In line with this finding, our study results showed smoking does not affect treatment outcomes or acute and chronic toxicity reactions. However, we did not investigate whether smoking status and cessation impact on patient survival. This could serve as a future extension of our research on this topic.

There is currently no consensus on the relationship between alcohol consumption and lung cancer incidence, as well as whether alcohol is one of the factors influencing lung cancer treatment outcomes (22). Our study results indicate that alcohol consumption does not affect the efficacy and acute or chronic toxicity reactions of SABR treatment for oligometastatic lung cancer.

We may have limited understanding of whether BMI effects on treatment outcomes and acute and chronic toxicity. However, some studies indicate that BMI is a factor influencing the efficacy and toxicity of SABR treatment. Overweight NSCLC patients treated with immune checkpoint inhibitors tend to have longer overall survival compared to those with normal weight (25). Additionally, one research has found that patients with low BMI might be more prone to severe toxic reactions, such as radiation pneumonitis and esophagitis. High BMI patients, on the other hand, may exhibit better tolerance to these treatments under certain conditions (26). However, we did find research about the relationship between BMI and radiotherapy. Our results indicate that patient BMI does not influence these results, which may be related to the relatively small size of our observational sample or BMI cannot replace the role of patients' nutrition condition.

The research of Islam et al. and Halvorsen et al. explained that different comorbid conditions were associated with worse outcomes and worse survival (27) (28). However, Halvorsen et al. demonstrated that patients with comorbidities successfully completed entire courses of chemotherapy and radiation therapy, with no significant differences observed in response rates, progression-free survival, or overall survival compared to the control group. Our study results did not observe a significant impact of multimorbidity on treatment outcomes either. This suggests that, as long as pre-existing conditions such as hypertension, diabetes, hyperlipidemia are well-controlled, elderly patients with multimorbidity can still undergo SABR without affecting treatment efficacy.

Regarding the number of metastases suitable for SABR treatment, there is considerable variation among different studies. However, a previous study suggests that treatments should be considered for patients with five or fewer metastases, or for those with fewer than three metastases within a single organ (29). Our study results indicate no significant differences in treatment efficacy and acute and chronic toxicity for patients with different number of metastases. However, since our study did not include cases with four or five metastases, future research could involve observing a larger cohort of patients with up to five metastases to investigate whether different outcomes are observed.

Lancia's study reviewed the outcomes of SABR in treating 70 elderly patients with solitary body metastases from different primary tumors. The results indicated excellent local control of the treated lesions, with a 87% of local control rates at 2 and 3 years. Additionally, the overall survival and disease-specific survival at 2 and 3 years were favorable. Only a few cases experienced grade ≥2 acute and chronic toxicity (4 cases with grade ≥2 acute toxicity and 6 cases with grade ≥2 chronic toxicity). The findings demonstrate that SABR is a safe and effective treatment modality for elderly patients with oligometastases who are considered unsuitable for systemic therapy (18). Our research findings are similar to those of Lancia, treatment outcomes for elderly patients with oligometastatic lung cancer are favorable, with minimal acute and chronic toxicity. Synchronous metastasis is defined as cancers occurring within 6 months after the first primary cancer, while metachronous cancers are defined as cancers occurring after 6 months. Compared to metachronous metastases, synchronous metastases are considered to have a poorer prognostic value. However, reports on this topic are scarce and contradictory (30) (31). Our study compared the treatment outcomes and acute and chronic toxicities of SABR in treating synchronous oligometastasis and metachronous oligometastasis, and we did not observe significant differences. Therefore, this can provide a basis for future related research, indicating that SABR can be selected for both synchronous and metachronous oligometastasis.

In a study of a five-fraction SABR regimen for centrally located NSCLC in an elderly population. Among 88 patients, only one experienced grade 5 toxicity, three experienced grade 3 toxicity, and all other toxicity reactions were below grade 3. This indicates that elderly patients can tolerate SABR treatment well and that the treatment has a high safety profile (32). The findings of this study are also validated by our research, showing no significant difference in toxicity reactions between elderly and younger patients, indicating that elderly patients can complete and adhere to the treatment regimen.

6. Limitations of this study and prospects for future research

Our sample size was small, with only 65 cases in total, of which 35 were aged 70 and above. This limited sample size may have hindered our ability to detect certain subtle effects. Second limitation, since all participants were recruited from Hospital Universitari Sant Joan de Reus, it is possible that our study design could be affected by selection bias, as they may share certain common underlying characteristics that could influence our study results, maybe a multicenter study could be more appropriate The third limitation of this study is the imbalance in characteristics between the two groups, when analyzing certain influencing factors, we observed that in some subgroups, the number of cases is very small or even zero, with most cases concentrated in another category. For example, when analyzing the impact of lung cancer histology late toxicity reactions between two groups, most cases are concentrated in NSCLC, while the number of SCLC cases is very small, and in some instances, there are zero cases of chronic toxicity which may result in an inability to observe the effects of influencing factors on treatment outcomes and acute and toxicity reactions.

Therefore, further research is warranted to investigate the impact of various factors on treatment outcomes and acute/late toxicity reactions in our study. Looking ahead, we could expand this research to multiple medical centers in the future, including a larger and more diverse patient population, to mitigate these potential biases and enhance the generalizability of the study findings.

7 Conclusion

Our results show that SABR is a good treatment option for older patients, demonstrating neither increased toxicity nor worse clinical responses. The treatment tolerance, treatment response, and toxicity are similar to those in the population under 70 years old. The study will continue with a larger number of patients and extended follow-up periods.

In this study, the anthropometric variables, comorbidities, toxic habits, and family history of cancer did not influence treatment response and toxicity. However, these factors could be studied in more detail in future research.

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