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Sterotactic Ablative radiotherapy in a Multicentric series of Oligometastatic SCLC: the SAMOS cohort

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Sterotactic Ablative radiotherapy in a Multicentric series of Oligometastatic SCLC: the SAMOS cohort

Short running title

Use of SBRT in Oligometastatic Small Cell Lung Cancer

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Conflict of Interest Statement

None

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Data Availability Statement for this Work

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

MICRO ABSTRACT

We conducted a retrospective multicentric analysis of patients with oligometastatic Small Cell Lung Cancer (SCLC) treated with Stereotactic Ablative Radiotherapy (SABR) from 2017 to 2022. Our findings suggest that

SABR may delay the need for additional treatments and extend ongoing treatment in oligometastatic SCLC, with the need for prospective studies to confirm these results.

ABSTRACT

Aims: SCLC is the most aggressive lung cancer histology with a 5-year OS <10%. At the diagnosis, almost two-thirds of the SCLC an Extended Disease presentation. Two randomized studies (CASPIAN and ImPower133) demonstrated an OS improvement, when immunotherapy was prescribed as maintenance therapy after standard chemotherapy. To date, SABR has had a limited indication in managing metastatic SCLC, although recent reports proposed it as a valid treatment option in selected patients. We propose a retrospective multicentric analysis of patients treated with SABR for oligometastatic SCLC.

Method: Data of patients affected by oligometastatic-SCLC treated with SABR between 2017 and 2022 in eleven Italian Centres were collected. Clinical and therapeutic variables together with OS and time to next treatment were analyzed. Univariate analysis with Kaplan–Meier curve were calculated, and log-rank test were applied. Cox proportional hazard model was used for multivariate analysis.

Results: Data from 93 patients and 132 metastatic lesions were analyzed. The median age was 64 years [36 – 86] and all but one had Performance Status 0 or 1. 52 patients presented ED at diagnosis. The first line treatment was radiochemotherapy in 42%, CHT alone in 24% and CHT-IO in 28%, others treatment accounts for 4% and only 2% of patients underwent best supportive care. Of the 132 lesions treated with SBRT 55 were in brain, 27 in lung, 11 in liver, 10 in lymph nodes, 8 in bones and 20 in adrenal gland. Median OS was 14 months, 1 year-OS and 2 years OS were 53% and 27%, respectively. The median TtNT was 14 months for the entire population. Of all the analysed variables only the anatomical site of the metastases and their number showed statistical significance in the univariate analysist, confirmed in the subsequent multivariate.

Conclusion: SABR seems to play a role in delaying further systemic lines in oligometastatic disease and to extend the use of ongoing treatment in oligoprogressive state. Prospective studies are needed to confirm these findings.

1. INTRODUCTION

Small Cell Lung Cancer (SCLC) accounts for about 14% of lung malignancies [1]. It is a very aggressive neoplasm characterized by a high growth fraction and early metastatic spread [2]. Approximately 250,000 new cases and at least 200,000 deaths are estimated each year for this cancer [3]. Smoking is the main risk factor and chronic obstructive pulmonary disease (COPD) is a common comorbidity [4]. SCLC has a particularly high mortality rate. Data extracted from the US Surveillance, Epidemiology, and End Results (SEER) American registry confirm a median survival between 1983 and 2021 of only 7 months [5]

Approximately two-thirds of patients diagnosed with SCLC have metastatic disease, classified as stage IV according to the American Joint Committee on Cancer (AJCC) or extended stage (ES) as defined by the Veterans Affairs Lung Study Group (VALSG) [6]. ES-SCLC has been recently investigated in two randomized trials exploring the role of immunotherapy combined with platinum end etoposide chemotherapy. The ImPower 133 study and the CASPIAN study have demonstrated to increase the median survival to about 13 months using atezolizumab and durvalumab, respectively [7], [8]

Radiotherapy (RT) plays a fundamental role in the ES-SCLC setting and specifically in the therapeutic option of prophylactic cranial irradiation (PCI) as an alternative to brain magnetic resonance surveillance [6]. Furthermore, thoracic RT is strongly recommended in selected patients with ES-SCLC after chemotherapy. At the same time, it remains conditional in those responding to chemotherapy combined with immunotherapy due to the absence of robust evidence [6]. Finally, the role of RT in the treatment of metastases remains consolidated with particular reference to the reduction of pain and neurological symptoms in patients with bone and brain secondary lesions [6]. Recently, some data are emerging about the role of consolidative thoracic RT in patients responding to first line chemo-immunotherapy demonstrating how a local approach may ameliorate the results in terms of clinical outcomes [9].

For many tumors, including lung cancer, there is growing evidence of the efficacy of ablative treatments in the management of metastases. Stereotactic ablative radiation therapy (SABR) is a highly focused radiation

treatment that delivers an elevated dose of radiation in few fractions (from 1 up to 8) while limiting the dose to surrounding organs. The role of SABR is particularly significant in the so-called oligometastatic setting defined by Hellman and Weichselbaum in 1995 as a state of mild and indolent disease dissemination [10], [11] There is an increasing availability of preclinical, translational, and clinical data that confirm the oligometastatic state and suggest the genetic, epigenetic and immunological interactions of metastatic neoplasia [10]. Despite this, a universal definition of oligometastatic disease is still under discussion because it tends to undergo different interpretative nuances, for example concerning the different histology and site of the primary tumor or the presence or absence of brain disease and systemic treatments on going. Furthermore, the number of metastases and organs involved assume a primary significance for the correct classification of oligometastatic disease [12]. Beyond these controversies, in the field of SCLC, the application of the concept of oligometastatic disease and the consequent use of stereotactic radiotherapy is rather infrequent due to the poor prognosis of the disease and the high capacity to develop multiple metastases.

, Recently a cohort study of 710 patients treated with SRS for SCLC brain metastases has provided a baseline for the encouraging results of stereotactic radiosurgery and has suggested that this treatment is a potential option for selected patients [13]. These findings have been confirmed in a subsequent review and meta-analysis [14].

Although oligometastatic state is particularly rare in SCLC, overall survival, progression free survival and pattern of recurrence of these patients are better in comparison to polymetastatic patients and the use of local treatment may result in a better prognosis [15].

This study aims to evaluate a multicentric series of patients treated with SABR on intracranial and extracranial metastases from SCLC. The objectives of this study are to primarily describe the clinical context in which the stereotactic treatment is proposed and the selection of patients to which it is offered. Secondly, the study aims to evaluate the prognostic impact and the consequent therapeutic effects.

2. MATERIAL AND METHODS

This observational study is based on a multicentric national database including 11 centers. Demographic, clinical, and therapy data were retrospectively collected from 1st January 2017 to 31st December 2022. All the centers obtained approval from their institutional review board after the coordinating center's ethical committee approved this study *("Anonymized for Review").*

At *"Anonymized for Review",* the presence of a written informed consent for the use of anonymized clinical data for research purposes was verified for every patient screened for the analysis.

Patients enrolled in the study had to meet the following inclusion criteria: age ≥ 18 years, histological proven diagnosis of SCLC, stage IV according to AJCC classification VIII edition or ES according to VALSG classification, compliance with the definition of "oligometastases" or "oligoprogression" according to EORTC i.e. ≤5 metastases in ≤3 organs (excluding mediastinal lymph nodes). Moreover, SABR had to be performed on some or all metastatic sites with a maximum of 8 fractions and a minimum dose per fraction equal to 5 Gy. Finally, patients were eligible if the staging procedure was performed according to good clinical practice and international guidelines. At baseline, all LS-SCLC patients received contrast-enhanced whole-body CT and 18-FDG CT-PET, whereas for ES-SCLC patients 18 FDG CT-PET was not mandatory. To define the oligometastatic state, brain MRI was always performed in case of suspicion of brain metastases on CT and 18-FDG CT-PET was requested when total body CT was doubtful or unclear for the numbering of metastatic lesions.

Clinical and therapy variables analysed were: age, gender, performance status (PS – ECOG), VALSG and AJCC – TNM stage, oligometastatic state, total dose of RT, fractionation, site and number of the treated metastases and use of prophylactic cranial irradiation (PCI).

General clinical outcomes were described using frequency, mean, median and range parameters. The overall survival (OS) and time to next treatment (TtNT) were defined as time between start of stereotactic treatment and death for any cause or start to new medical treatment or best supportive care, respectively. For the univariate analysis the Kaplan–Meier curve were calculated, and log-rank test were applied to compare groups. Cox proportional hazard model was used for multivariate analysis, including significant

variables at univariate analysis. All hypothesis tests were 2-sided and a $p < 0.05$ was considered statistically significant.

SPSS® Statistics (IBM®, Armonk, New York, USA) version 24 was used for statistical analysis.

3. RESULTS

Data from 93 patients were collected with 132 lesions treated. At the time of the diagnosis the median age was 64 years (36-86 years) and 52.7% of the patients were male; PS- scale was 0 in the 58.1% of the patients and 1 in 40.9% of patients. 44.1% of the patients had LS-SCLC at the first presentation, while 55.9% had ES-SCLC. Only 10.8% of the patients had stage I or II of disease according to TNM - AJCC 8th edition. Brain and lung metastases were the most frequently treated lesions, 41.7% and 20.4% of the cases, respectively.

A synchronous oligometastatic disease was observed in 23.7% of the patients, metachronous oligometastatic in 35.5% and oligoprogressive in 40.9% of cases.

Age at the time of SABR		
	Median 64 years	Range 36 – 86
Gender		
	Male	49 (52.7%)
	Female	44 (47.3%)
PS - ECOG		
	0	54 (58.1%)
	1	38 (40.8%)
	2	1 (1.1%)
VALSG stage at the diagnosis		

LS-SCLC	41 (44.1%)
ES-SCLC	52 (55.9%)
TNM-AJCC stage at the diagnosis	
Stage I	1 (1.1%)
Stage II	9 (9.7%)
Stage III	38 (40.8%)
Stage IV	45 (48.4%)
Oligometastatic state	
Synchronous Oligometastatic	22 (23.7%)
Metachronous Oligometastatic	33 (35.5%)
Oligoprogressive	38 (40.8%)
Total dose of SABR (Gy)	
Mean 31.6	Range 18 – 60
Dose/fraction of SABR (Gy/fraction)	
Mean 10.7	Range 5 – 25
Site of metastasis	
Brain	55 (41.7%)
Lung	27 (20.4%)
Liver	11 (8.3%)
Bone	8 (6 %)
Lymph node	10 (7.5%)
Adrenal gland	20 (15.4%)
Others	1 (0.7%)
Number of treated metastases	

	1	43 (46.2%)
	>1	50 (53.8%)
	PCI	
Yes		37 (39.8%)
No		56 (60.2%)

Table 1. Patients', disease and treatment characteristics (SABR= Stereotactic Ablative Radiotherapy; PS-ECOG = Performance Status according to Eastern Cooperative Oncology Group; VALSG = Veterans Administration Lung Cancer Study Group; LS-SCLC = Limited Stage Small Cell Lung Cancer; ES-SCLC = Extended Stage Small Cell Lung Cancer; SABR= Stereotactic Ablative Radiotherapy; Gy = Gray; PCI = Prophylactic cranial irradiation).

A wide heterogeneity of SABR fractionations was observed in this retrospective cohort, the mean total dose and mean dose per fraction were 31.6 Gy and 10.7 Gy/fraction respectively. The most common treatment schedule registered for brain metastases was 24 Gy in 3 fractions, for lung lesions it was 48 Gy in 3 fractions or 45 Gy in 3 fractions, for bone metastases 30 Gy in 3 fractions. For lymph node lesions, the most used fractionation was 30 Gy in 6 fractions, while liver and adrenal metastases did not have a standard schedule and were treated with different fractions and doses among the participating centers. A single lesion was treated in 46.2% of the cases.

The 39.8% of the patients had received prophylactic cranial irradiation (PCI) among the treatments for SCLC.

All clinical and therapy related variables are summarized in Table 1.

Forty-two percent of patients underwent chemo-radiotherapy (RT-CHT); 23.5% received chemotherapy alone and 28% chemo-immunotherapy; finally, 4.3% of patients underwent other, unspecified, treatments. Only 2 patients (2.2%) received best supportive care (BSC). While CHT-RT is the most widely used treatment in first line, this percentage decreased in second (1.1%) and third line (0%). The percentage of patients undergoing BSC in the second (60.3%) and third line (79.6%) progressively increased (Figure 1).15 patients

received an additional stereotactic treatment after the first recorded one, with a total number of 33 metastases treated.

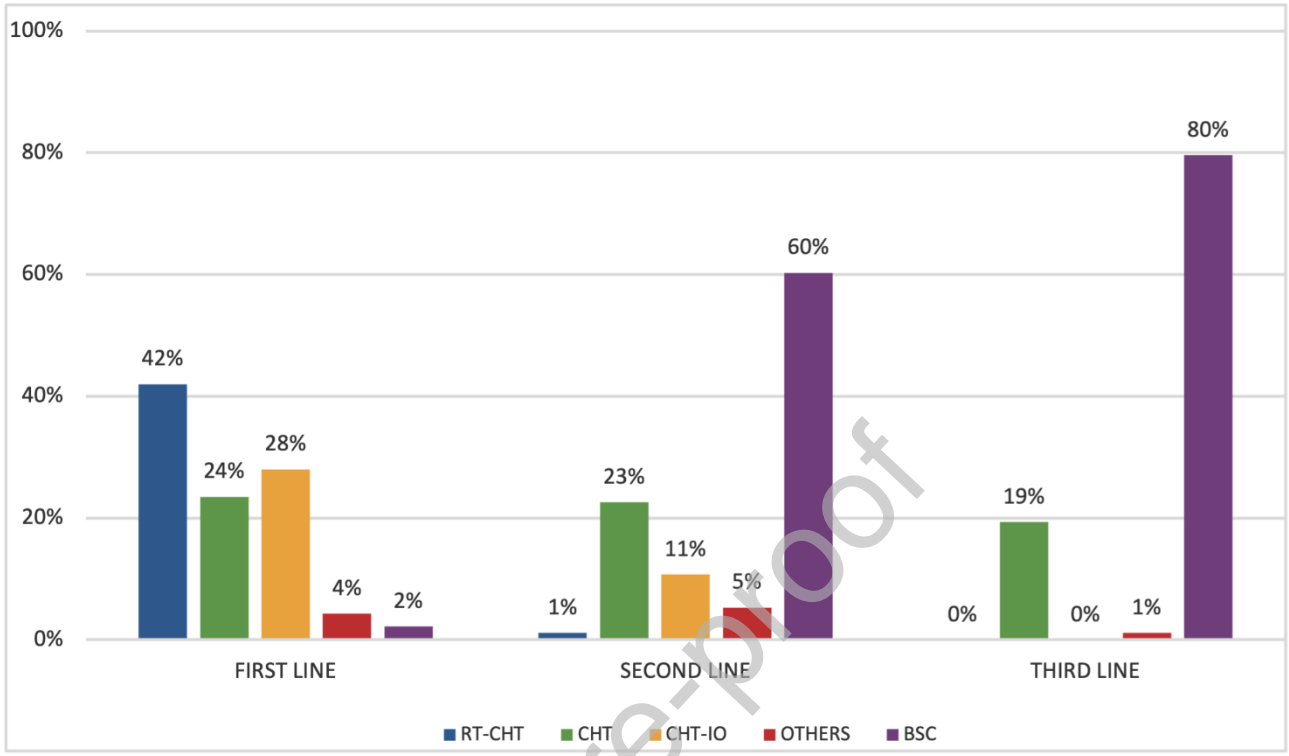

Figure 1: Systemic treatment distribution. (RT-CHT= Chemo-radiation therapy; CHT= chemotherapy; CHT-IO= Chemo-immunotherapy; BSC= best supportive care).

The median, 1-year and 2-years OS of the entire series were 14 months, 53% and 27%, respectively.

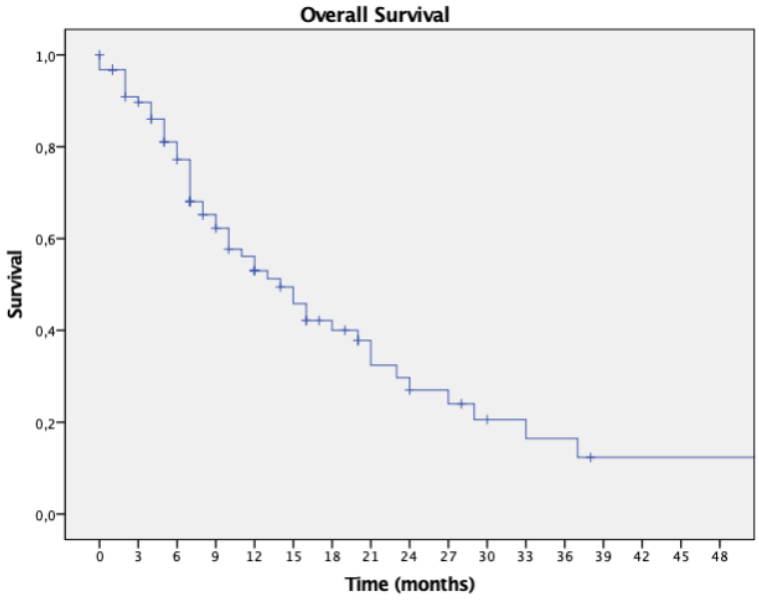

Figure 2: Kaplan - Meier curve of entire population's OS

Median OS was higher for synchronous oligometastasis and 2-yrs OS was lower for oligoprogressive SCLC. The median TnNT resulted 8.8 months. The OS and TnNT for all cases and for patients grouped according oligometastatic state are reported in Table 2.

	Median OS (months)	1-year OS	2-year OS	Mean TtNT (months)	TtNT Range (months)
Synchronous Oligomet	16	50.5%	35.4%	10.2	0 - 58
Metachronous Oligomet	12	58.3%	34%	9	0 - 37
Oligoprogressive	14	50.6%	14.8%	7.5	0 - 59
Total population	14	53%	27%	8.8	0 - 60

Table 2: Overall-Survival and Time to Next Treatment in the three group of patients and in the total population. (OS = Overall Survival; TtNT = Time to Next Treatement)

Within all the considered variables, the site and number of treated metastases showed a statistical significance at the univariate analysis. Median OS for brain vs no brain metastasis was 9 months and 20 months, respectively (P = 0.009). Median OS for patients treated for 1 or more metastases resulted 21 months and 10 months, respectively (p =0.014). These findings were confirmed at the multivariate analysis. Results are summarized in Table 3.

	UNIVARIATE ANALYSIS			***MULTIVARIATE ANALYSIS***		
		median OS (months)	***p***	**HR**	**CI**	***P***
Age	<65 years	15	NS	-	-	-
	≥ 65 years	15				
Gender	Female	13	NS	-	-	-
	Male	16				
PS - ECOG	0	18	NS	-	-	-
	1-2	11				
VALS Stage	LS	16	NS	-	-	-
	ES	13				
Oligometastatic	SyO	16	NS	-	-	-

		UNIVARIATE ANALYSIS		*MULTIVARIATE ANALYSIS*		
		median OS (months)	***p***	**HR**	**CI**	***P***
State	MeO	12				
	OlP	14				
Site of metastasis	Brain	9	0,009	0,495	0,281 - 0,845	0,011
	No Brain	20				
Number of treated metastasis	1	21	0,014	2,031	1,141 - 3,617	0,016
	>1	10				
PCI	Yes	18	NS	-	-	-
	No	10				

Table 3: Univariate and multivariate analysis of the categorial variables of the population (OS = Overall Survival; LD = Limited Stage Disease; ED = Extended Stage Disease; PS - ECOG = Performance Status; SyO = Synchronous Oligometastatic; MeO = Metachronous Oligometastatic; OlP= Oligoprogressive; PCI = Prophylactic Cranial Irradiation; HR = Hazard Ratio; CI= Confidence Interval)

4. DISCUSSION

To our knowledge, this cohort represents the first large series with 93 oligometastatic SCLC patients treated with SABR. Recently, the results of a similar multicentre retrospective study of 20 patients has been reported . The authors' findings showed an excellent local control in a cohort of oligoprogressive/oligorecurrent SCLC patients with extracranial disease despite a rare durable response after SBRT [16] .

The poor prognosis associated with SCLC, combined with the limited potential to treat this population, has reduced the interest and availability of data in this scenario, in contrast to the overwhelming growth of data supporting the use of stereotactic treatment in many oligometastatic malignancies [17], [18]

The recent introduction of immunotherapy in the setting of ES-SCLC has shown a modest but valuable survival benefit. The Caspian and Impower133 studies reported a similar and significant increase in median OS [7], [8]

This slight benefit, of about 3 months, does not dramatically change the prognosis of ES-SCLC but it has rekindled the clinical and scientific interest for the SCLC.

To date, it is still unclear which patients will really benefit of adding immunotherapy to chemotherapy and the current discussion focuses on patients' selection criteria and predictive biomarkers to identify the best candidates to the combined treatment [19].

Stereotactic radiotherapy with ablative intent has found wide consensus and growing application in oligometastatic malignancies, initially for those with more indolent behaviour and subsequently also for more aggressive ones [20]–[23]

With the recent advent of immunotherapy in ES-SCLC, traditional approaches to this particular disease setting are being revised. Historically, ablative treatment of metastases has played an extremely marginal role in SCLC. Indeed, patients with brain metastases from SCLC were excluded from randomized clinical

trials that established SRS alone as a first-line strategy in lung cancer, making SCLC an exception where whole brain RT remained the standard of care for limited and even solitary brain metastases.

Notably, the combination of SABR with target therapies and immunotherapy has covered a crucial role in scientific research and clinical practice in lung cancer. Unfortunately, this improvement did not translate with the same impact in the limited field of SCLC. Furthermore, for many cohort studies and trials evaluating the role of SABR, the SCLC histology was even represented as an exclusion criterion [24].

Scientific evidence has so far described SABR as a non-invasive treatment able to prolong progression-free survival and sometimes overall survival, independently of the different cancers [25]–[27]

SABR may also reduce tumor burden, prevent progression to polymetastatic state and alleviate associated morbidity and mortality [28]

Finally, it is clearly defined its potential role in delaying further systemic lines in oligometastatic disease and to extend the use of ongoing treatment in oligoprogressive state [29], [30].

Given the above cited considerations, it is possible to suggest that SABR in oligometastatic SCLC could be considered as an option, in particular in the era where immune checkpoint inhibitor, combined with chemotherapy, has become the new standard. A combination of radio-immunotherapy originates from the significant immune-stimulatory effects they exert boosting the natural antitumor immune response.

SABR and immunotherapy are both responsible of maturation and proliferation of naive T-cells activating a synergistic effect. Moreover, SABR through the release of neo-antigens may increase the tumoricidal effect of chemo-immunotherapy combination [31]–[33].

This experience shows that SABR in synchronous/metachronous oligometastatic and oligoprogressive SCLC is a feasible and effective option to be considered in selected patients. The median OS of 14 months after SABR in the entire series is strongly encouraging if considered the registrative trials that reported a median OS of 12,3 and 13 months with Atezolizumab and Durvalumab, respectively. Interestingly, similar benefits were reported in this series within subgroups with different oligometastatic scenarios. Indeed, the OS shown in synchronous, metachronous and progressive oligometastases varied between 12 and 16 months

without statistical significance. This could mean that, despite the different clinical presentation, oligometastatic SCLC has a peculiar and homogeneous clinical behavior.

Brain metastasis and multiple lesions seem to predict a worse prognosis; however, the FIRE-SCLC cohort study suggest that stereotactic radiosurgery did not negatively affect OS if compared to whole brain radiotherapy [14].

Because of our cohort's large variety of anatomical sites and fractionations, we did not analyze the toxicities that may have occurred after or during the stereotactic treatment. However, SABR has already demonstrated high feasibility with a low incidence of acute and late toxicities, and all the fractionations used were already reported in the literature [25], [34], [35]

Finally, it should be noted that the OS reported in this study follows that of the RTOG 0937 study. This randomized phase 2 trial, although not adopting sterotactic radiotherapy for oligometastases, investigated the role of PCI in combination or not with thoracic consolidation in ES -SCLC with 1 to 4 metastases, thus reflecting the same population selection as the present cohort. In the RTOG study, 1-year OS ranged between 50% and 60%, consistent with the results of this analysis [36].

Despite the retrospective nature of this series, it represents a valid benchmark for future, hopefully, prospective studies. Furthermore, this analysis allows for profiling a particular subset of biologically and clinically favored ES-SCLC patients. This should lead to the reflection that perhaps not all patients with ES-SCLC are marked by a poor prognosis and that, therefore, multidisciplinary and personalized management could improve in clinical outcomes.

5. CONCLUSIONS

This cohort analyzes the effect of SABR exclusively on oligometastatic ES-SCLC patients. The large number of patients and lesions that entered our study establishes that SABR is a feasible treatment for these selected and rare patients who may benefit from this treatment in terms of OS and TTnT. These findings should lead the way to realize prospective and larger trials.

6. AKNOWLEDGMENT

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BIBLIOGRAPHY

[1] Z. Megyesfalvi *et al.*, "The landscape of small cell lung cancer metastases: Organ specificity and timing," *Thorac Cancer*, vol. 12, no. 6, pp. 914–923, Mar. 2021, doi: 10.1111/1759-7714.13854.

[2] G. P. Kalemkerian *et al.*, "NCCN Guidelines Insights: Small Cell Lung Cancer, Version 2.2018," *J Natl Compr Canc Netw*, vol. 16, no. 10, pp. 1171–1182, Oct. 2018, doi: 10.6004/JNCCN.2018.0079.

[3] F. Bray, B. Kohler, and J. Ferlay, *Cancer Incidence in Five Continents Volume X*. International Agency for Research on Cancer, 2014. Accessed: May 23, 2023. [Online]. Available: http://www.iacr.com.fr/.

[4] Rudin, Charles M et al. "Small-cell lung cancer." *Nature reviews. Disease primers* vol. 7,1 3. 14 Jan. 2021, doi:10.1038/s41572-020-00235-0

[5] S. Wang *et al.*, "Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages," *Sci Rep*, vol. 7, no. 1, Dec. 2017, doi: 10.1038/S41598-017-01571-0.

[6] C. B. Simone *et al.*, "Radiation Therapy for Small Cell Lung Cancer: An ASTRO Clinical Practice Guideline," *Pract Radiat Oncol*, vol. 10, no. 3, pp. 158–173, May 2020, doi: 10.1016/J.PRRO.2020.02.009.

[7] L. Horn *et al.*, "First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer," *N Engl J Med*, vol. 379, no. 23, pp. 2220–2229, Dec. 2018, doi: 10.1056/NEJMOA1809064.

[8] L. Paz-Ares *et al.*, "Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial," *Lancet*, vol. 394, no. 10212, pp. 1929–1939, Nov. 2019, doi: 10.1016/S0140-6736(19)32222-6.

[9] G. Guaitoli *et al.*, "Dissecting Immunotherapy Strategies for Small Cell Lung Cancer: Antibodies, Ionizing Radiation and CAR-T," *International Journal of Molecular Sciences*, vol. 23, no. 21. MDPI, Nov. 01, 2022. doi: 10.3390/ijms232112728.

[10] Gutiontov, Stanley I et al. "Oligometastasis: Past, Present, Future." *International journal of radiation oncology, biology, physics* vol. 108,3 (2020): 530-538. doi:10.1016/j.ijrobp.2020.02.019

[11] S. Hellman and R. R. Weichselbaum, "Oligometastases," *J Clin Oncol*, vol. 13, no. 1, pp. 8–10, 1995, doi: 10.1200/JCO.1995.13.1.8.

[12] S. Otake and T. Goto, "Stereotactic Radiotherapy for Oligometastasis," *Cancers (Basel)*, vol. 11, no. 2, Jan. 2019, doi: 10.3390/CANCERS11020133.

[13] C. G. Rusthoven *et al.*, "Evaluation of First-line Radiosurgery vs Whole-Brain Radiotherapy for Small Cell Lung Cancer Brain Metastases: The FIRE-SCLC Cohort Study," *JAMA Oncol*, vol. 6, no. 7, pp. 1028–1037, Jul. 2020, doi: 10.1001/JAMAONCOL.2020.1271.

[14] K. Gaebe *et al.*, "Stereotactic radiosurgery versus whole brain radiotherapy in patients with intracranial metastatic disease and small-cell lung cancer: a systematic review and meta-analysis," *Lancet Oncol*, vol. 23, no. 7, pp. 931–939, Jul. 2022, doi: 10.1016/S1470-2045(22)00271-6.

[15] M. Shirasawa *et al.*, "Prognostic differences between oligometastatic and polymetastatic extensive disease-small cell lung cancer," *PLoS One*, vol. 14, no. 4, Apr. 2019, doi: 10.1371/JOURNAL.PONE.0214599.

[16] Levy, Antonin et al. "Stereotactic body radiotherapy for extra-cranial oligoprogressive or oligorecurrent small-cell lung cancer." *Clinical and translational radiation oncology* vol. 41 100637. 3 May. 2023, doi:10.1016/j.ctro.2023.100637

[17] Guerrero, Eduardo, and Merina Ahmed. “The role of stereotactic ablative radiotherapy (SBRT) in the management of oligometastatic non small cell lung cancer.” *Lung cancer (Amsterdam, Netherlands)* vol. 92 (2016): 22-8. doi:10.1016/j.lungcan.2015.11.015

[18] D. Lisowski *et al.*, “Health-related quality of life and clinical outcome after radiotherapy of patients with intracranial meningioma,” *Sci Rep*, vol. 12, no. 1, Dec. 2022, doi: 10.1038/s41598-022-24192-8.

[19] M. Mino-Kenudson *et al.*, “Predictive Biomarkers for Immunotherapy in Lung Cancer: Perspective From the International Association for the Study of Lung Cancer Pathology Committee,” *J Thorac Oncol*, vol. 17, no. 12, pp. 1335–1354, Dec. 2022, doi: 10.1016/J.JTHO.2022.09.109.

[20] L. Triggiani *et al.*, “Efficacy of stereotactic body radiotherapy in oligorecurrent and in oligoprogressive prostate cancer: new evidence from a multicentric study,” *Br J Cancer*, vol. 116, no. 12, pp. 1520–1525, Jun. 2017, doi: 10.1038/BJC.2017.103.

[21] J. Kobiela *et al.*, “Ablative stereotactic radiotherapy for oligometastatic colorectal cancer: Systematic review,” *Crit Rev Oncol Hematol*, vol. 129, pp. 91–101, Sep. 2018, doi: 10.1016/J.CRITREVONC.2018.06.005.

[22] Guerrero, Eduardo, and Merina Ahmed. “The role of stereotactic ablative radiotherapy (SBRT) in the management of oligometastatic non small cell lung cancer.” *Lung cancer (Amsterdam, Netherlands)* vol. 92 (2016): 22-8. doi:10.1016/j.lungcan.2015.11.015

[23] T. Watanabe *et al.*, “Deep abscopal response to radiotherapy and anti-PD-1 in an oligometastatic melanoma patient with unfavorable pretreatment immune signature,” *Cancer Immunol Immunother*, vol. 69, no. 9, pp. 1823–1832, Sep. 2020, doi: 10.1007/S00262-020-02587-8.

[24] D. A. Palma *et al.*, “Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial,” *J Clin Oncol*, vol. 38, no. 25, pp. 2830–2838, 2020, doi: 10.1200/JCO.20.00818.

[25] Patel, P H et al. “The Dandelion Dilemma Revisited for Oligoprogression: Treat the Whole Lawn or Weed Selectively?.” *Clinical oncology (Royal College of Radiologists (Great Britain))* vol. 31,12 (2019): 824-833. doi:10.1016/j.clon.2019.05.015

[26] D. A. Palma *et al.*, “The oligometastatic state - separating truth from wishful thinking,” *Nat Rev Clin Oncol*, vol. 11, no. 9, pp. 549–557, 2014, doi: 10.1038/NRCLINONC.2014.96.

[27] C. Collen *et al.*, “Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients,” *Ann Oncol*, vol. 25, no. 10, pp. 1954–1959, Oct. 2014, doi: 10.1093/ANNONC/MDU370.

[28] R. Olson *et al.*, “Quality of Life Outcomes After Stereotactic Ablative Radiation Therapy (SABR) Versus Standard of Care Treatments in the Oligometastatic Setting: A Secondary Analysis of the SABR-COMET Randomized Trial,” *Int J Radiat Oncol Biol Phys*, vol. 105, no. 5, pp. 943–947, Dec. 2019, doi: 10.1016/J.IJROBP.2019.08.041.

[29] L. M. Wintner *et al.*, “Quality of life during chemotherapy in lung cancer patients: results across different treatment lines,” *Br J Cancer*, vol. 109, no. 9, pp. 2301–2308, Oct. 2013, doi: 10.1038/BJC.2013.585.

[30] R. A. Vilela *et al.*, “Use of stereotactic body radiation therapy for oligometastatic recurrent prostate cancer: A systematic review,” *J Med Imaging Radiat Oncol*, vol. 62, no. 5, pp. 692–706, Oct. 2018, doi: 10.1111/1754-9485.12747.

[31] R. Mazzola *et al.*, “Oligometastasis and local ablation in the era of systemic targeted and immunotherapy,” *Radiat Oncol*, vol. 15, no. 1, May 2020, doi: 10.1186/S13014-020-01544-0.

[32] Ngwa, Wilfred et al. “Using immunotherapy to boost the abscopal effect.” *Nature reviews. Cancer* vol. 18,5 (2018): 313-322. doi:10.1038/nrc.2018.6

[33] Weichselbaum, Ralph R et al. “Radiotherapy and immunotherapy: a beneficial liaison?.” *Nature reviews. Clinical oncology* vol. 14,6 (2017): 365-379. doi:10.1038/nrclinonc.2016.211.

[34] C. Menichelli *et al.*, "Stereotactic radiotherapy for liver oligometastases," *Rep Pract Oncol Radiother*, vol. 27, no. 1, pp. 32–39, 2022, doi: 10.5603/RPOR.A2021.0130.

[35] L. Kuntz *et al.*, "Acute toxicities and cumulative dose to the brain of repeated sessions of stereotactic radiotherapy (SRT) for brain metastases: a retrospective study of 184 patients," *Radiation Oncology*, vol. 18, no. 1, pp. 1–12, Dec. 2023, doi: 10.1186/S13014-022-02194-0/TABLES/6.

[36] EM. Gore et al. "Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extracranial Irradiation for Extensive-Disease Small Cell Lung Cancer (ED SCLC): NRG Oncology RTOG 0937". J Thorac Oncol. 2017;12(10):1561-1570. doi:10.1016/j.jtho.2017.06.015

CLINICAL PRACTICE POINTS

Small Cell Lung Cancer (SCLC) is a highly aggressive and deadly form of lung cancer, with a limited range of treatment options. Recent studies have demonstrated some improvement in overall survival (OS) through the introduction of immunotherapy in the extended-stage (ES) SCLC setting.

Stereotactic Ablative Radiotherapy (SABR) has shown potential in managing metastases, particularly in the oligometastatic state characterized by limited and indolent disease spread. However, its application in SCLC has been limited due to the disease's poor prognosis and propensity for multiple metastases.

Recent evidence suggests that SABR, especially for brain metastases, can be effective for selected SCLC patients.

This study analyzed data from 93 SCLC patients treated with SABR for intracranial and extracranial metastases.

The results showed that SABR may extend overall survival, particularly for patients with brain metastases and fewer treated lesions.

Despite the retrospective nature of the study, it serves as an essential benchmark for potential prospective research.

The introduction of immunotherapy in ES-SCLC has generated renewed interest in the disease, but challenges remain in selecting the right candidates for combined treatment.

Stereotactic treatments like SABR have demonstrated efficacy in managing metastases, offering potential benefits in OS and time to next treatment.

These findings encourage further investigation and prospective trials to refine patient selection criteria and optimize the use of SABR, potentially improving outcomes for SCLC patients.

This study underlines the importance of personalized and multidisciplinary approaches to ES-SCLC management, challenging the notion of a uniformly poor prognosis and paving the way for more tailored therapies.