Revista do Grupo de Estudos do Cancro do Pulmão

VOL. XX, N.º 1; 2023

ISSN 1645-9466

GRUPO de ESTUDOS do CANCRO do PULMÃO

Página da Direção

A humanização na doença oncológica

Maria Teresa Almodovar[1]

[1] Serviço Pneumologia Instituto Português Oncologia Lisboa, Lisboa, Portugal

Novembro é o mês internacionalmente escolhido para a sensibilização para o Cancro do Pulmão. Previsivelmente várias entidades e grupos (entre os quais o GECP) vão desenvolver campanhas para consciencializar a população para esta doença, sintomas, fatores de risco e para os benefícios de adoção de uma vida saudável.

Enquanto pensava no tema da página da direção para este número da revista prévio ao mês de Novembro, deparei-me com o editorial da Lancet deste mês[1] que aborda o tema da humanização na abordagem do cancro. O Editorial inicia com a seguinte abordagem: Um doente oncológico. Um caso de cancro. Termos comuns, mas que podem ter um grande impacto nos doentes e na sua saúde mental. Usando uma linguagem de doença como esta, pode-se desumanizar o doente, equiparando-o à sua doença, em vez de se referir a ele como um indivíduo.[1]

O impacto emocional de um diagnóstico de cancro, sobre um doente, membro da família ou amigo, depende das próprias experiências médicas e pessoais de um indivíduo e pode manifestar-se como depressão, ansiedade, stress, raiva ou uma combinação destes. O uso comum de linguagem centrada na doença, como *doente com cancro de pulmão*, denigre o doente e a sua jornada individual, equiparando o indivíduo à sua doença.[1]

O Cancro de Pulmão, frequentemente ligado a hábitos tabágicos, está, mais do que muitas outras doenças, ligado a sentimento de culpa da pessoa diagnosticada e a um estigma por parte da sociedade.

A linguagem médica clássica quer ao dirigir-se à pessoa com cancro, quer entre pares, remete para uma abordagem que anula a identidade pessoal de quem tem cancro, tornando-o apenas num portador de doença.

Na Conferência Mundial sobre Cancro de Pulmão da Associação Internacional para o Estudo do Cancro de Pulmão (IASLC), de 2023, o tema também foi abordado. Foi divulgado um **Guia de Línguas da IASLC**,[2] amplamente debatido, e promovidos os benefícios da sua implementação. Nele salienta-se a importância de usar a linguagem da pessoa em primeiro lugar eliminando a linguagem de culpa e acabando com o estigma. Foram apresentados vários exemplos práticos, como usar o termo pessoa com cancro do pulmão em vez de doente com cancro do pulmão, ou pessoa com uso ativo de tabaco em vez de fumador.

A culpa e o estigma estão muito enraizados na nossa sociedade e as mentalidades não se alteram apenas com um conjunto de boas intenções. É necessário desenvolver um trabalho de sensibilização junto da sociedade, das famílias e dos doentes, mas também junto dos profissionais de saúde. Temos de ter a consciência que esta mudança pode demorar anos. No entanto penso que compete a nós, médicos e outros profissionais de saúde que tratam pessoas com cancro do pulmão ajudar a alterar esta situação na sociedade e na prestação de cuidados diminuindo o estigma sobre as pessoas com o diagnóstico de cancro do pulmão.

Estamos nós médicos portugueses cientes deste problema e seremos capazes de mudar?

BIBLIOGRAFIA

1. Editorial www.thelancet.com/oncology Vol 24 October 2023 https://www.thelancet.com/action/showPdf?pii=S1470-2045%2823%2900465-5
2. https://www.iaslc.org/IALCLanguageGuide

ORCID

Maria Teresa Almodovar 0000-0001-8950-2100

Editorial

2013 e a imunoterapia em neoadjuvância no estádio precoce

Fernando Barata[1]

[1] Departamento Oncologia Centro Hospitalar Universitário Coimbra, Coimbra, Portugal

Diagnosticamos 20% a 25% dos nossos doentes em estádio precoce. Para eles, historicamente, a cirurgia isolada ou combinada com quimioterapia e pontualmente com radioterapia era a opção terapêutica. A sobrevida aos cinco anos ultrapassava, em média, pouco mais de 60%.

Desde há décadas pensamos como melhorar este quadro. Definir melhores biomarcadores, aumentar a ressecabilidade, melhor diversificar e combinar opções terapêuticas, aumentar a resposta patológica, eliminar a doença micro-metastática ou minimizar segundos cancros são estratégias para obter este objetivo.

Todos conhecemos os resultados, na doença avançada, da inclusão da imunoterapia e das terapêuticas alvo no arsenal terapêutico. Onde no passado tínhamos 5% a 10% a cinco anos, temos hoje 15% a 20%.

Com a abordagem neoadjuvante procuramos um tratamento imediato das micrometastases subclínicas enquanto que com a abordagem adjuvante procuramos eliminar células tumorais residuais após a cirurgia e mitigar a taxa de recidiva da doença.

Em 2021 e 2022 conversámos sobre os resultados positivos da terapêutica adjuvante com Atezolizumab (IMPOWER 010) e Pembrolizumab (PEARLS). O ano de 2023 ficará como o ano da neoadjuvância em cancro do pulmão precoce.

O estudo de fase III, CHECKMATE 816, avaliou nivolumab com dupleto de platina (3 ciclos) em doentes com estádio IB a IIIA ressecável e demonstrou um claro benefício na sobrevida livre de eventos, independente da expressão de PDL1 favorecendo a quimio/imunoterapia com 31,6 meses *versus* 20,8 meses para a quimioterapia. Também a taxa de resposta patológica completa foi de 24% *versus* 2,2%.

Também o estudo de fase III AEGEAN com recurso a quimio/imunoterapia peri operatória mostra para estádios IIA a IIIB, uma sobrevida livre de eventos não atingida com durvalumab e quimioterapia *versus* 25,9 meses com a quimioterapia. A taxa de respostas patológicas completas é de 17,2% para o braço durvalumab e quimioterapia *versus* 4,3% para o braço sem durvalumab.

O estudo KEYNOTE 671 também peri operatório, em estádios II a IIIB mostra uma sobrevida livre de eventos não atingida com pembrolizumab *versus* 17 meses apenas com a quimioterapia. A taxa de

http://doi.org/10.32932/gecp.2023.10.041

resposta patológica completa foi de 18,1 % para o braço com pembrolizumab *versus* 4,0% para o braço sem imunoterapia.

Múltiplos estudos, com imunoterapia associada a quimioterapia, em contexto neoadjuvante e adjuvante mostram hoje resultados preliminares muito promissores. Ano após ano, estamos a conseguir melhorar a sobrevida global dos nossos doentes. Vamos continuar.

ORCID

Fernando Barata 0000-0002-6306-0938

Artigo de Revisão

Brief fatigue inventory as a fatigue identification scale in lung cancer patients under immunotherapy – A real-life study

Mariana Picado[1], Carina Gaspar[1], Maria Teresa Almodovar[1]

[1] Department of Pulmonology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal
* marianacpicado@gmail.com

ABSTRACT

Introduction: Lung cancer (LC) is one of the most frequent oncological diseases in the world, and the use of immunotherapy is a substantial progress regarding new therapeutic options. Fatigue is the most frequently reported adverse effect in patients starting immunotherapy treatment, but it remains underdiagnosed. The purpose of this study was to identify whether the assessment of fatigue, recorded by the clinical team in the pulmonology consultation, agrees with that reported by patients with Non-Small Cell Lung Cancer (NSCLC), when answering the *Brief Fatigue Inventory* (BFI) questionnaire during treatment with immunotherapy alone or in combination with chemotherapy.
Methods: A prospective observational study was conducted over 8 months. The research took place through the collection of medical records from the clinical files of the patients and the application of the BFI questionnaire, before each of 4 treatment cycles. **Results:** The sample consisted of 31 patients with 26 males and 5 females, with a mean age of 68.5 years. The mean value of the BFI score before the 1st treatment, as well as in the following 3 evaluations, was higher for the participants who presented symptoms of asthenia/tiredness/fatigue recorded in the clinical files at the consultation and lower for those who did not. However, the differences were not statistically significant (pre 1st treatment- *p=0.299,* pre 2nd treatment- *p=0.125,* pre 3rd treatment- *p=0.103* and pre 4th treatment- *p=0.954).* By comparing the BFI questionnaire score with the medical records, we found that fatigue remained underreported in the consultation at the different evaluation moments (75.9% of the sample participants were not identified with fatigue at the 1st moment of evaluation; 75% at the pre-2nd treatment consultation; 81.2% at the pre-3rd treatment consultation and 88.9% at the pre-4th treatment consultation).
Conclusions: The benefit of applying the BFI questionnaire was relevant. This tool allowed the identification and stratification of fatigue, demonstrating greater sensitivity when compared only with the medical records of the consultation. The fact that the study sample was small was a limitation and made it difficult to obtain more robust results. Therefore, it is desirable to carry out more prospective, long-term studies in this area, to consolidate the results found in the present investigation.

Key words: non-small cell lung cancer; immunotherapy; adverse effects; fatigue; medical records; *brief fatigue inventory*

INTRODUCTION

LC is currently considered one of the most frequent oncological diseases in the world, diagnosed mainly after 65 years, with a median age close to 70 years. This cancer, composed of a considerable histological and molecular diversity, is divided into two main groups, Non-Small Cell Lung Cancer (NSCLC), constituting approximately 85% of cases and Small Cell Lung Cancer (SCLC) with a representativeness of about 15%[1]

The treatment of PC has undergone remarkable progress in recent decades, regarding the development of new therapies aimed at this pathology.[2] In patients with stage IV NSCLC, the therapeutic option is based on systemic therapy, equated according to the histological result, tumor genetics, expression of Programmed Cell Death Ligand 1 (PD L1), comorbidities, age, and patient preference.[3]

Immunotherapy has a prominent place as therapeutic option in patients with LC. Nevertheless, this treatment may develop adverse effects of which fatigue stands out.[4] This symptom, which has an extremely significant impact on patients' quality of life, is often undervalued and underdiagnosed despite being one of the most prevalent adverse effects related to LC and its treatment.[5] The use of symptom auto assessment instruments is extremely important to systematize and standardize procedures, to clarify the communication between the health professional and the patient, promoting an improvement in the quality of health care.[6] The fatigue assessment scale, BFI, is an instrument for assessing this symptom that presents a high reliability and internal consistency, consisting of 9 questions on a scale from 0 to 10. It assesses the severity of fatigue and its effects on patients' ability to perform their activities of daily living in the last 24 hours. It is a short questionnaire and assesses fatigue in a one-dimensional way. The overall score can be obtained through the average of all responses to the questionnaire, ranging from 0 to 10. Thus, absent fatigue is considered if the score is 0, mild fatigue between 1-3.99, moderate between 4-6.99 and severe 7-10. [7,8]

The purpose of this study is to evaluate whether fatigue is properly identified by clinicians in LC consultations, comparing the fatigue reported by patients by filling out the BFI questionnaire periodically, with the evaluation made by the physician in the consultation, through the records in the clinical files of the patients, during the period of treatment with immunotherapy.

METHODS

Study population

An observational study with a prospective design was conducted between March 4, 2022, and November 30, 2022. The study participants were selected in the multidisciplinary consultation of thoracic tumors of the Department of Pulmonology of the Portuguese Institute of Oncology of Lisbon, Francisco Gentil (IPO). All patients with NSCLC stage II or IV proposed for treatment with immunotherapy in monotherapy in 1st or 2nd line or treatment of 1st line in combined regimen with chemotherapy were included.

Al patients that were invited to participate signed an informed consentient. Study was approved by the local ethical board.

Methodology of data collection

Sociodemographic data, characterization of the disease, comorbidities and factors associated with fatigue and analytical results were collected through consultations of the participants' clinical processes. Patients completed the BFI questionnaires.

Statistical analysis

Descriptive statistics were used to describe the characteristics of the study population. The variables measured in Likert scale were analyzed through the categories presented with description of some relevant statistics such as the mean, the standard deviation, the coefficient of variation and the minimum and maximum values observed. To evaluate the relationship of two qualitative variables, Fisher's test and Student's t parametric test were used *to* study quantitative variables and a dichotomous variable. To study the relationship between quantitative variables and a qualitative variable, the ANOVA parametric test was used and the degree of correlation between two quantitative variables was measured using Pearson's correction coefficient. Finally, the t-test for paired samples was used to evaluate the differences in a variable measured at two moments for the same elements of the sample. Statistical analysis and graphical representations were performed using IBM® SPSS® Statistics software version 27, considering a 95% confidence interval.

RESULTS

The sample consisted of 31 patients, 26 males (84%) and 5 females (16%). The mean age was 68.5 years with a standard deviation of 8.7 years. Regarding smoking habits, 7% were non-smokers, 30% smokers and 63.3% former smokers. In this study, 13 patients received pembrolizumab therapy, 5 patients received nivolumab therapy and 13 patients received IQT therapy. Regarding treatment lines, 83.9% were 1st line of treatment and 16.1% the 2nd line of treatment. Regarding number of treatments, 6 underwent only 1 treatment cycle (interruption due to disease progression), 2 patients underwent 3 treatment cycles, 1 patient underwent 2 cycles and 2 patients underwent 3 treatment cycles. A total of 20 patients underwent the 4 proposed treatment cycles. The mean value of the BFI score before the 1st treatment, as well as in the following 3 evaluations, was higher for the participants who presented symptoms of asthenia/tiredness/fatigue recorded in the clinical files at the consultation and lower for those who did not. However, the differences were not statistically significant (pre 1st *treatment- p=0.299- table 1, pre 2nd treatment- p=0.125, table 2, pre 3rd treatment- p=0.103- table 3 and pre 4th treatment-*

Table 1. Baseline assessment – Pre 1st treatment

	Asthenia/Tiredness/Fatigue				t	p
	No (N=29)		Yes (N=2)			
	M	SD	M	SD		
BFI baseline score	3,23	2,93	5,50	2,91	-1,058	0,299

Table 2. Pre 2nd treatment evaluation

	Asthenia/Tiredness/Fatigue				t	p
	No (N=20)		Yes (N=5)			
	M	SD	M	SD		
BFI pre 2nd treatment score	3,00	2,14	4,71	2,20	-1,591	0,125

Table 3. Pre 3nd treatment evaluation

	Asthenia/Tiredness/Fatigue				t	p
	No (N=16)		Yes (N=8)			
	M	SD	M	SD		
BFI pre 3rd treatment score	3,82	2,56	5,76	2,82	-1,699	0,103

Table 4. Pre 4nd treatment evaluation

	Asthenia/Tiredness/Fatigue				t	p
	No (N=9)		Yes (N=11)			
	M	SD	M	SD		
Yes (N=11)	5,88	2,63	6,00	3,14	-0,059	0,954

p=0.954- table 4). By comparing the BFI questionnaire score with the medical records, it was found that fatigue remained underreported in the consultation at the different evaluation moments (75.9% of the sample participants were not identified with fatigue at the 1st moment of evaluation; 75% at the pre-2nd treatment consultation; 81.2% at the pre-3rd treatment consultation and 88.9% at the pre-4th treatment consultation).

DISCUSSION

The purpose of this study was to optimize the monitoring of fatigue caused by immunotherapy, reported by the patient, to contribute to the improvement in the quality of life of cancer patients. As for the main objective, the assessment of fatigue identified by the physician in the consultation compared with the evaluation of each BFI questionnaire, deserves an individualized interpretation in the different treatment cycles. Regarding this correspondence, *the p* values in the statistical tests used differed, but it was not possible to obtain statistically significant results. Regarding the survey used, it is important to note that this proved to be an instrument capable of identifying different stages of fatigue, and it is particularly important to highlight the easy access in its completion.

Thus, it is possible to admit that the selected scale was adequate as an instrument to measure fatigue in this sample. Analyzing the 4 moments of pre-treatment evaluation, it was possible to verify that fatigue always remained underreported by the doctor in the consultation in a percentage greater than or equal to 75%. Thus, a congruent evolution of the mean BFI *score* was identified in relation to the evidence in terms of the expected time for the development of fatigue during the treatment cycles of patients with NSCLC, reaching a higher mean value in the pre-4th treatment evaluation, which corresponds approximately to the 12th week after the beginning of the therapeutic cycles with IO or IQT. The results also suggest that this tool is sensitive in the identification of fatigue not reported in the consultation, as well as in the stratification of different degrees of severity, namely in moderate and severe cases. The main limitations of this study were the small sample size, 31 patients. Some of the participants died before the end of the study, which contributed to the increased complexity of the statistical analysis of the results.

In conclusion, fatigue is a multifactorial symptom that should be carefully monitored to improve the patient's quality of life and consequently maintain compliance with NSCLC treatment.

With regard to future research, it is desirable to conduct a greater number of long-term prospective studies to assess fatigue, preferably with different fatigue measurement instruments, with a larger number of participants, in order to consolidate the results found in this research.

ORCID

Mariana Picado 0000-0001-7516-119X
Carina Gaspar 0000-0002-8679-6104
M Teresa Almodovar 0000-0001-8950-2100

REFERENCES

1. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, *68*(6), 394–424. https://doi.org/10.3322/caac.21492.

2. Hoy, H., Lynch, T., & Beck, M. (2019). Surgical Treatment of Lung Cancer. *Critical care nursing clinics of North America*, *31*(3), 303–313. https://doi.org/10.1016/j.cnc.2019.05.002.
3. Planchard, D., Popat, S., Kerr, K., Novello, S., Smit, E. F., Faivre-Finn, C., Mok, T. S., Reck, M., Van Schil, P. E., Hellmann, M. D., Peters, S., & ESMO Guidelines Committee (2018). Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology*, *29*(Suppl 4), iv192–iv237. https://doi.org/10.1093/annonc/mdy275.
4. Su, C., Wang, H., Liu, Y., Guo, Q., Zhang, L., Li, J., Zhou, W., Yan, Y., Zhou, X., & Zhang, J. (2020). Adverse Effects of Anti-PD-1/PD-L1 Therapy in Non-small Cell Lung Cancer. *Frontiers in oncology*, *10*, 554313. https://doi.org/10.3389/fonc.2020.554313.
5. Portenoy, R. K., & Itri, L. M. (1999). Cancer-Related Fatigue: Guidelines for Evaluation and Management. *The Oncologist*, *4*(1), 1–10.https://doi.org/10.1634/theoncologist.4-1-1.
6. Paramita, N., Nusdwinuringtyas, N., Nuhonni, S. A., Atmakusuma, T. D., Ismail, R. I., Mendoza, T. R., & Cleeland, C. S. (2016). Validity and Reliability of the Indonesian Version of the Brief Fatigue Inventory in Cancer Patients. *Journal of pain and symptom management*, *52*(5), 744–751. https://doi.org/10.1016/j.jpainsymman.2016.04.011.
7. Suleiman, K., Al Kalaldeh, M., AbuSharour, L., Yates, B., Berger, A., Mendoza, T., Malak, M., Salameh, A. B., Cleeland, C., & Menshawi, A. (2019). Validation study of the Arabic version of the Brief Fatigue Inventory (BFI-A). *Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit*, *25*(11), 784–790. https://doi.org/10.26719/emhj.19.032.
8. Ahlberg, K., Ekman, T., Gaston-Johansson, F., & Mock, V. (2003). Assessment and management of cancer-related fatigue in adults. *Lancet (London, England)*, *362*(9384), 640–650. https://doi.org/10.1016/S0140-6736(03)14186-4.

Stereotactic Body Radiation Therapy (SBRT): An optimal approach in the treatment of lung cancer and pulmonary metastases – a Portuguese center experience

Inês Félix Pinto[1,*], Tomás Cabral Dinis[1], Leonor Martins[1], Inês Nobre-Góis[1], Filipa Vinagre[1], Ana Cleto[1], Margarida Borrego[1]

[1] Radiotherapy Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
* 11852@chuc.min-saude.pt

RESUMO

A radioterapia estereotáxica corporal (SBRT) é um método não-invasivo, seguro e eficaz no tratamento do cancro do pulmão de estadio inicial e em lesões pulmonares secundárias, em doentes selecionados. Embora não exista consenso na dose ideal e esquema de fracionamento, uma dose biológica efetiva (BED) ≥100 Gy está associada a um aumento significativo do controlo local e sobrevivência. O objetivo deste estudo é analisar os esquemas de fracionamento, toxicidade e sobrevivência de doentes com doença pulmonar primária e secundária, tratados com SBRT de Janeiro/2016 a Dezembro/2021 no nosso centro. Toxicidade avaliada segundo escala CTCAE 5.0 e a análise de sobrevivência com método Kaplan–Meier. Incluídos 90 doentes (110 tumores) com idade mediana 71 anos e Karnofsky ≥90% em 74,4%. 42 doentes (43 tumores) tinham cancro do pulmão, a maioria adenocarcinoma (76,2%), cT1b-cN0 (66,7%) e com tumores periféricos (83,7%) de tamanho mediano 20,5mm (8-50). 48 doentes (67 tumores) tinham lesões pulmonares secundárias, maioritariamente de cancro colorretal (66,7%), 70,1% tumores periféricos de tamanho mediano 11,5 mm (4-43 mm). Quanto a toxicidade, registou-se: 8,9% com pneumonite (grau 1/2), 11,1% com dor torácica e 5,6% com fratura de costela (grau 1). Tempo de follow-up mediano de 22 meses. Na doença pulmonar primária, a taxa de controlo tumoral (TC), sobrevivência global (OS) e sobrevivência livre de doença (DFS) aos 2 anos foi de 84,6%, 71,6% e 51,4%. Na doença pulmonar secundária, registou-se TC de 86,8%%, OS de 74% e DFS de 34,4% aos 2 anos. SBRT é um tratamento bem tolerado e com resultados favoráveis.

Palavras-chave: Radioterapia, SBRT, Cancro do pulmão, Metástases pulmonares

ABSTRACT

Stereotactic Body Radiation Therapy (SBRT) is a noninvasive, safe, and effective treatment for early-stage lung cancer and metastatic lung disease in selected patients. Although there is no current consensus on the ideal dose

and fractionation schedule for pulmonary SBRT, intensive regimens of BED ≥100 Gy are associated with significantly better local control and survival.The purpose of this study was to analyze fractionation schedules, toxicity and survival outcomes in patients with early-stage lung cancer and lung metastases treated with SBRT between January 2016 – December 2021 in our center. Toxicity was evaluated using CTCAE v5.0 and survival outcomes by the Kaplan–Meier method. We included 90 patients (110 tumors total) with a median age of 71 years and Karnofsky Performance Status≥90% in 74,4%. 42 patients (43 tumors) had early-stage primary lung cancer, mostly adenocarcinoma (76,2%), stage cT1b-cN0 (66,7%) and peripheral tumors (83,7%) with a median size of 20,5mm (8-50). 48 patients (67 tumors) had secondary lung disease mostly from colorectal cancer (66,7%), 70,1% were peripheral tumors with a median size of 11,5 mm (4-43 mm). Regarding toxicity, 8,9% of patients had pneumonitis (grade 1 and 2), 11,1% reported chest pain and 5,6% had rib fracture (grade 1). Median follow up was 22 months. In primary lung cancer, the 2-year tumor control (TC), overall survival (OS) and disease free survival (DFS) was 84,6%, 71,6% and 51,4%, respectively. Patients with lung metastases had a 2-year TC of 86,8%%, OS of 74% and DFS of 34,4%. SBRT is a well tolerated treatment option with favorable outcomes.

Keywords: Radiotherapy; SBRT; Lung cancer; Lung metastases.

INTRODUCTION

Lung cancer is the second most common cancer in both men and women and the leading cause of cancer related death[1]. The lung is also one of the most frequent sites of metastization - around 20–54% of cancer patients have lung metastases at some point during the course of their disease[2].

According to the most recent international guidelines, stereotactic body radiation therapy (SBRT) is recommended for patients with non-small cell lung cancer (NSCLC) stage I and II (cT1–3N0M0) who are medically inoperable[3]. SBRT can also be considered in lung metastases, on an oligometastatic setting, with improvement in OS as shown in recent studies. The maximum number of lesions for ablative therapy has yet to be determined[4,5].

Over the past 2 decades, technological developments in target delineation, motion management, conformal treatment planning, and daily image guidance have allowed development and implementation of this technique, which uses ablative and highly conformal radiation doses delivered to limited size targets, while minimizing toxicity to surrounding tissues[6,7].

There is no current consensus on the ideal dose and fractionation for SBRT in lung lesions. However, one aspect that is uncontested is the need to achieve a high biologically effective dose (BED) of ≥100 Gy[6].

Central vs peripheral tumors

It is known that the location of the tumor can influence toxicity rates when specific SBRT dose-fractionation schedules are used. The widely accepted ASTRO definition, describes a central tumor as a tumor located within 2 cm of the proximal tracheobronchial tree, otherwise it is considered a peripheral tumor[7]. Other definitions, such as the one in the RTOG 0813 protocol, includes on the central tumor definition any tumor with location within 2 cm of the mediastinal structures such as heart, major vessels and esophagus[8].

Primary lung cancer

For patients with operable early-stage NSCLC, SBRT is not proven equivalent to lobectomy. The only two randomized phase 3 trials (STARS and ROSEL) that compared SBRT to lobectomy did not complete accrual. A pooled analysis of these two trials showed higher 3-year OS after SBRT compared to surgery (95% vs 79%, p=0·037) and similar 3-year recurrence-free survival (86% vs 80%, p=0.54)[9]. Later, a report of the long-term results of the revised STARS trial showed no significant difference in OS[10]. Other smaller studies have shown similar overall survival and cancer-specific survival[11,12]. This does not provide sufficient data to change the standard of care, but it is promising and confirms that SBRT is an alternative to surgery for patients with potentially operable disease who are high risk surgical patients or who refuse surgery.

Also, compared to conventionally fractionated radiation therapy (RT), SBRT has achieved higher local control rates and OS[7]. The phase III multicentric Australian TROG/ALTG randomized trial (CHISEL) compared SBRT (54Gy/3Fr or 48Gy/4Fr) with conventional RT (66Gy/33Fr or 50Gy/20Fr) and showed improved local control and OS with SBRT, with low toxicity[13]. The Scandinavian randomized trial (SPACE) also compared SBRT (66Gy/3Fr) with conventional RT (70Gy/35Fr) and showed similar local control and OS, but lower incidence of pneumonitis and oesophagitis with SBRT[14].

Regarding treatment of lung lesion with SBRT, most studies included mainly peripheral tumors, where common fractionation schedules are 48Gy/4fr, 54Gy/3fr or single fractions (30-34Gy).

The RTOG 0236 was the first North American multicenter phase II trial to test SBRT in medically inoperable patients with peripheral early-stage NSCLC. The prescription dose was 54 Gy/3Fr and showed high local control rates, with 5-year primary failure of 7% and moderate treatment related morbidity (toxicity grade 3 in 27% and grade 4 in 3%)[15]. This fractionation schedule was also evaluated in patients with operable NSCLC with similarly high rate of primary tumor control and infrequent need for surgical salvage[16].

Singh et al., assessed 30 Gy/1 fr vs. 60 Gy/3 fr and showed no significant difference in local control, progression free survival (PFS) or OS, but better social functioning and less dyspnea with the single fraction treatment[17].

Another important study, the RTOG 0915 phase II trial, evaluated two schedules (34 Gy /1Fr vs 48 Gy/4 Fr) with primary tumor failure at 5 years of 10.6% vs 6.8%, and acute effects in 10.3% vs 13.3%, respectively[18].

For central tumors there is limited prospective evidence. RTOG 08-13 was a multicentre phase II study that assessed the safety and efficacy of a five fraction schedule (dose range of 50Gy--60Gy) for central NSCL tumors. The 3-year local control and OS was 75%, with no grade 3 toxicity. Higher doses per fraction were associated with improved efficacy but also increased risk of severe toxicities[8].

The 8-fraction schedule (such as 60Gy/8Fr) is commonly used particularly in Europe and Canada. Kimura et al. (phase I trial) evaluated 5 dose levels (52Gy to 60Gy) in 8 fractions and determined the recommended dose of 60Gy with acceptable efficacy and toxicity rates[19]. Also, a systematic review suggests that treatments with BED 10Gy ≥100 Gy and BED 3Gy ≤210 Gy, such as 60 Gy in 8 fractions, result in acceptable efficacy and toxicity rates[20]. The ongoing SUNSET trial evaluates the 60Gy/8fr in central and ultra-central tumors[21].

Secondary lung lesions

In secondary lung lesions, metastasectomy is the historical treatment, but it requires medically

fit patients with adequate general conditions as well as cardiovascular and respiratory functions. Therefore, SBRT started to be used as a curative option in patients unsuitable for surgery based on the favorable results in NSCLC[22]. on the metastatic setting it has also demonstrated excellent local control rates, with 2-year local control 91-96%, depending on histologic subtype. The first randomized trial for treatment of pulmonary oligometastases was SAFRON II, where patients with 1-3 pulmonary peripheral metastases received either single a 28 Gy fraction or 48 Gy in 12 Gy fractions (on non-consecutive days over 2 weeks). There was no significant difference for local control or treatment related grade ≥3 adverse effects[23].

There is limited information regarding efficacy and safety of central lesions in the context of oligometastatic disease. Patients with central disease were excluded of SAFRON II.

MATERIALS AND METHODS

We retrospectively reviewed patients treated with SBRT in our center between January 2016 and December 2021.

We included patients with NSCLC stage I - II (cT1–3N0M0) histology proven who were medically inoperable or refused surgery, and patients with lung metastases documented on PET-CT or CT scan, maximum tumor size of 5 cm and a minimum follow-up of 1 year.

Four dimensional computed tomography (4DCT) with abdominal compression was acquired in most patients for treatment planning and cone beam computer tomography (CBCT) was acquired before and after each treatment.

With regards to volume delineation, gross tumor volume (GTV) was contoured on CT images (1 mm thickness); clinical target volume (CTV) was considered to be the same as GTV; internal target volume (ITV) was contoured according to the respiratory motion of the tumor; planning target volume (PTV) was defined as a 5 mm isotropic margin from the ITV.

Dose was prescribed according to location, size, performance status and OARs dose constraints. For central lesions prescription dose was 60Gy/8fr (7,5Gy/fr) and for peripheral lesions doses ranged between single fraction (25-34Gy), 40Gy/3Fr, 45Gy/3fr (15Gy/fr), 48Gy/4fr (12Gy/fr), 50Gy/5fr (10Gy/fr) 60Gy/8fr (7,5Gy/fr) and 70Gy/10fr (7Gy/fr).

All treatments were planned for a TrueBeam linear accelerator equipped with a Millennium MLC and calculated with 6MV FFF photon beams with a 1.0 mm dose grid size, and AAA eclipse algorithm. Volumetric Arc Therapy (VMAT) was used on all treatment plans using a PTV coverage primary goal of V100% > 95%. Organs at risk (OAR) dose constraints were mostly based on the RTOG 0813 and 0915 protocols and AAPM Report 101 (American Association of Physicists in Medicine).

After treatment, patients were followed every 3 months the first 2 years and every 6 months thereafter. Imaging with CT scan or 18F-FDG PET/CT was used to assess treatment response.

Tumor control (TC) was defined as the absence of increased tumor dimension or SUV max in imaging assessment response (CT scan or 18F-FDG PET/CT), disease free survival (DFS) was the time from beginning of treatment to lack of tumor control, regional failure, distant metastasis or disease related death, and overall survival (OS) was defined as the time from beginning of treatment to date of death from any cause. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Survival rates and curves were calculated by the Kaplan–Meier method.

This study was approved by the ethical committee responsible.

RESULTS

We analyzed 90 patients with a total of 110 tumors/lesions: 42 patients with early stage lung cancer and 48 with lung metastasis. The baseline characteristics of the patients are shown in Table 1 and 2.

Regarding primary lung cancer, mostly were staged IA2 (31%) and IA3 (35,7%) who were considered high risk for or refused surgery. Biopsy was performed in all of them, with adenocarcinoma being the most common histology (76,2%). We treated a total of 43 tumors (1 patient had two tumors), with a median size of 21 mm (8-50). All central tumors were prescribed 60Gy/8Fr (BED10Gy = 105Gy). Peripheral tumors were given 48Gy/4Fr (BED10Gy = 105,6Gy) in 75% and 50Gy/5Fr (BED10Gy =100 Gy) in 19,4%. Characteristics are summarized in Table 3.

Concerning the forty eight patients with secondary lung disease, nineteen had two or more metastases that were treated separately with different PTVs, giving a total of sixty seven lesions, with a median size of 12 mm (4-43). The most frequent site of primary tumor was colorectal (66,7%) followed by lung disease(12,5%). Concerning fractionation schedules, all central lesions (n=20) were prescribed 60Gy/8Fr ((BED10Gy = 105Gy). Forty-

Table 1. General primary lung cancer patients characteristics (n=42)

Age (Years)		77 (53-90)
Gender	Masculine	59,5%
	Feminine	40,5%
KPS	90-100%	58,6%
	≤ 80%	41,4%
Smoker	Yes	52,9%
	No	47,1%
Staging AJCC 8th edition	cT1aN0M0	4,8% (n=2)
	cT1bN0M0	31% (n=13)
	cT1cN0M0	35,7% (n=15)
	cT2aN0M0	14,3% (n=6)
	cT2bN0M0	7,1% (n=3)
	cT3N0M0	7,1% (n=3)
Histology	Adenocarcinoma	76,2% (n=32)
	SCC	11,9% (n=5)
	Other[1]	11,9% (n=5)
Number of lesions treated per patient	1	97,6% (n=41)
	2	2,3% (n=1)
	3	–
	4	–

[1] Include: adenosquamous carcinoma, large cell neuroendocrine carcinoma.

Table 2. General lung metastases patients characteristics (n= 48)

Age (Years)		67 (16-90)
Gender	Masculine	64,6%
	Feminine	35,4%
Karnofsky	90-100%	88,9%
	≤ 80%	11,1%
Smoker	Yes	29%
	No	71%
Primary Tumor	CCR	66,7% (n=32)
	Lung	12,5% (n=6)
	Esophageal	4,2% (n=2)
	Ovarian	4,2% (n=2)
	Other[1]	12,5% (n=6)
Number of lesions treated per patient	1	62,5% (n=30)
	2	25% (n=12)
	3	10,4% (n=5)
	4	2,1% (n=1)

[1] Include: Prostate cancer, endometrial cancer, renal cell cancer, Ewing sarcoma, oral cavity cancer, laryngeal cancer.

Table 3. Primary lung cancer

		Central tumors (n=7)	Peripheral tumors (n=36)
Lung	Right	42,9% (n=3)	52,8% (n=19)
	Left	57,1% (n=4)	47,2% (n=17)
Lobe	Superior	57,1% (n=4)	66,7% (n=24)
	Medial	14,3% (n=1)	5,6% (n=2)
	Inferior	28,6% (n=2)	27,8% (n=10)
Size (mm)	Median	25	20,5
	Min.-Max.	15-46	8-50
Fractionation schedules	**70Gy/10Fr** BED_{10Gy} = 119 Gy	–	2,8% (n=1)
	60Gy/8Fr BED_{10Gy} = 105 Gy	100% (n=7)	–
	50Gy/5Fr BED_{10Gy} = 100 Gy	–	19,4% (n=7)
	48Gy/4Fr BED_{10Gy} = 105.6 Gy	–	75% (n=27)
	40Gy/3Fr BED_{10Gy} = 93.2 Gy	–	2,8% (n=1)
PTV (cc)	Median	45,9	29,4
	Min.-Máx.	11,6-78	4,7-115

Table 4. Lung metastases (n=67 lesions)

		Central lesions (n=20)	Peripheral lesions (n=47)
Lung	Right	60% (n=12)	66% (n=31)
	Left	40% (n=8)	34% (n=16)
Lobe	Superior	40% (n=8)	31,9% (n=15)
	Medial	15% (n=3)	8,5% (n=4)
	Inferior	45% (n=9)	59,6% (n=28)
Size (mm)	Median	17	11,5
	Min.-Max.	9-33	4-43
Fractionation schedules	**25Gy/1Fr** BED_{10Gy} = 87.5 Gy	–	2,1% (n=1)
	30Gy/1Fr BED_{10Gy} = 120 Gy	–	10,6% (n=5)
	34Gy/1Fr BED_{10Gy} = 149.6 Gy	–	8,5% (n=4)
	45Gy/3Fr BED_{10Gy} = 117 Gy	–	2,1% (n=1)
	48Gy/4Fr BED_{10Gy} = 105.6 Gy	–	48,9% (n=23)
	50Gy/5Fr BED_{10Gy} = 100 Gy	–	21,3% (n=10)
	60Gy/8Fr BED_{10Gy} = 105 Gy	100% (n=20)	6,4% (n=3)
PTV (cc)	Median	13,9	11,8
	Min.-Máx.	4,8-97,8	4,3-105

seven were peripheral lesions that were given mostly 48Gy/4Fr (BED10Gy = 105,6Gy) in 48,9% and 50Gy/5Fr (BED10Gy =100 Gy) in 21,3%. Other fractionation schedules, such as single fraction, were given according to metastases location and size and OARS dose constraints. Secondary lung lesions characteristics of are summarized in table 4.

In most cases all the OARs dose constraints were met. In peripheral tumors, the PTVs often overlap the ribs and therefore the rib optimal constraints were not considered.

All patients underwent their treatment as planned. Two patients presented acute adverse events (acute dermatitis and esophagitis, both grade 1). Regarding late adverse events, 9,2% of patients had pneumonitis (grade 1 and 2), 11,5% reported chest pain and 5,7% had rib fracture (grade 1). No grade ≥ 3 adverse events were observed.

The median follow up time was 22 months. In primary lung cancer, the 2-year tumor control (TC), disease free survival (DFS) and overall survival (OS) were 84,6%, 51,4% and 71,6% respectively (Figure 1). We obtained 46,5% complete clinical responses, 27,9% partial clinical responses (decreased tumor size and/or SUVmax) and 14% stabilized (maintained same tumor size and/or SUVmax). Two patients (4,8%) had local failure

Figure 1. Survival curves – primary lung cancer.

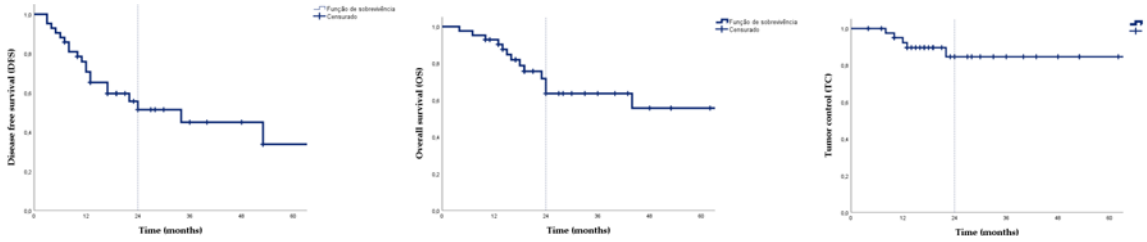
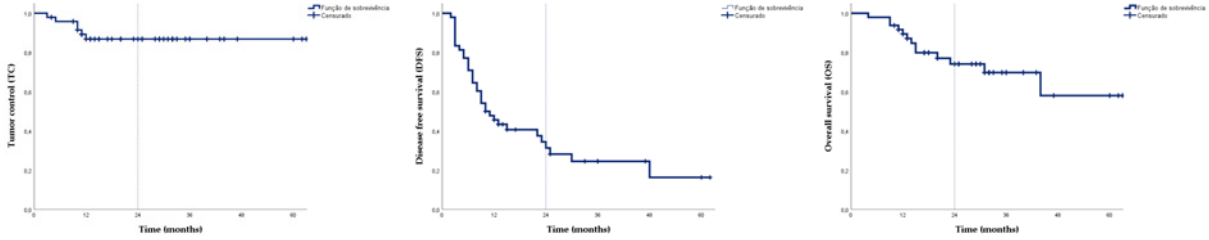


Figure 2. Survival curves – Secondary lung disease.



and fifteen (35,7%) had systemic pro-gression, mostly within the lung, the liver and the adrenal gland.

Patients with lung metastases had a 2-year TC of 86,8%, DFS of 34,4% and OS of 74% (Figure 2). In 53,7% of lesions we observed a complete clinical response, 16,4% a partial clinical response and 17,9% stabilized. Six patients (12,5%) experienced local failure and 27 patients (56,3%) systemic progression, with the most frequent site being lung and liver.

DISCUSSION

This study demonstrated that SBRT is a safe and an effective treatment option.

The optimal dose of SBRT has not yet been determined. Even though multiple fractionation schedules were used in previous studies, the results have been consistently favorable, with high local control and survival rates, while maintaining low toxicity.

In peripheral tumors we used mostly the 48Gy/4Fr and 50Gy/5Fr fractionation schedule. When we compare our results with the classic RTOG trials (0236, 0915, 0618) that report 3-year tumor control rates around 92-97% in primary lung cancer lesions, we have a slightly lower tumor control rate[15,16,18]. This can be due to the fact that these trials include a bigger proportion of cT1 tumors, whereas in our sample 28,5% of patients are cT2-3. Also, they only include peripheral tumors, while 16,3% of our sample of patients with primary lung cancer has central tumors, that were treated with a schedule with increased number of fractions (60Gy/8Fr) and hence a lower achievable BED. In fact, when we look at the RTOG 0813 results (for central tumors) the 2-year local control rate of 89,4% is closer[8].

In some cases, we were able to use single fractionation treatment schedules (25-34Gy). The-

re are 3 completed randomized phase 2 trials comparing single to mul-ti-fraction treatment schedules. Two (RTOG 0915, RPCI-124407) were conducted in medically inoperable early-stage lung cancer patients and have been fully published[18,24]. The third (SAFRON II) involves treatment of oligometastatic disease to the lungs[23]. They all used different single fraction schedules, with total dose ranging from 28Gy to 34Gy.

More evidence is emerging supporting single fraction when choosing SBRT schedules in peripheral tumors, since it shows similar outcomes but smaller overall treatment time, even in the absence of a phase 3 trial. In fact, it was the preferred option for treating peripheral early-stage NSCLC during the COVID-19 pandemic in a European Society for Radiotherapy and Oncology–American Society for Radiation Oncology consensus statement[25].

Regarding the group of patients with lung metastases, our study has comparable results with the SAFRON II trial. This trial reported results at 3-years with tumor control rates of 64% in the single fraction arm and 80% in the multi-fraction arm[23].

As described in literature, the predominant pattern of failure after treatment with SBRT is the development of distant metastases. Despite the high rates of local control in patients receiving commonly employed regimens of BED of 100 Gy or greater, local recurrence after SBRT can be seen in up to 20% in large series with long-term follow-up[26]. This is also compatible with our results, where in patients with primary lung cancer, 35,7% had systemic progression versus 4,8% who had local failure. Same in patients with secondary lung lesions where 56,3% developed other metastasis and 12,5% had local failure.

Regarding the size of the treated lesions, we established the consensual limit of a maximum 5 cm size[27]. For tumors above 5 cm SBRT can also be considered an appropriate option if acceptable dosimetric constraints are achievable. However, this applies to primary lung tumors, with conditional strength of recommendation and a low quality of evidence, so those were not included in this sample[7].

Regarding toxicity, we reported a low toxicity rate with pneumonitis (grade 1 and 2) in 9,2%, chest pain in 11,5% and rib fracture (grade 1) in 5,7%. These numbers are lower than in other studies since we didn't observe any grade 3 events. However, these results must be interpreted with caution because the retrospective nature of this data can lead to bias or underestimation.

Early studies demonstrated higher risk of severe toxicity (~50%) in the treatment of central tumors[28]. The often-quoted study by Timmerman et al. from Indiana University reported increased toxicities in patients with centrally located tumors treated with 60–66 Gy in 3 fractions; on multivariate analysis, tumor location was the strongest predictor for toxicity[29]. However, later studies have shown improved tolerability with the use of more protracted (e.g., 4 or more fractions) or lower BED schedules. Even though central tumors represent 24,5% of our entire sample, we didn't detect a statistically significant toxicity difference in patients with central tumors versus peripheral tumors. This can be due to a reduced number of events.

The main limitations of this study are related to its retrospective design, the variation in dose-fractionation schedules and the sample heterogeneity, as patients in the metastatic setting had tumors with different histologic subtypes, multiple primary tumor locations and the administered systemic therapy was made at the discretion of the assistant medical oncologist.

CONCLUSIONS

Outcomes from this study in regards to local control, survival rates and toxicity, are comparable to the ones from randomized trials. SBRT is achievable in routine practice and has been sustained over time. These data support the continued use of this technique in daily clinical practice.

ORCID

Inês Félix Pinto 0009-0002-5962-5067
Tomàs Cabral Dinis 0000-0002-3507-2966
Leonor Martins 0000-0003-2030-8072
Inês Nobre Gois 0000-0002-1497-8988
Filipa Vinagre 0009-0004-1589-0170
Ana Cleto 0000-0003-2811-204X
Margarida Borrego 0000-0002-9886-5971

REFERENCES

1. World Health Organization (WHO). Global Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2019. WHO; 2020. Accessed March 09, 2023.
2. Gutiérrez E, Sánchez I, Díaz O, et al. Current evidence for stereotactic body radiotherapy in lung metastases. Current Oncology. 2021;28(4):2560-2578. doi:10.3390/curroncol28040233
3. Kristina Gregory N, Miranda Hughes O, Aisner DL, et al. NCCN Guidelines Version 2.2023 Non-Small Cell Lung Cancer Continue NCCN Guidelines Panel Disclosures.; 2023. https://www.nccn.org/home/member-
4. Chan M, Palma D, Barry A, et al. Practical Considerations for the Implementation of a Stereotactic Body Radiation Therapy Program for Oligo-Metastases. Adv Radiat Oncol. 2021;6(1):100499. doi:10.1016/j.adro.2020.06.004
5. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol. 2020;21(1):e18-e28. doi:10.1016/S1470-2045(19)30718-1
6. Moreno AC, Fellman B, Hobbs BP, et al. Biologically Effective Dose in Stereotactic Body Radiotherapy and Survival for Patients With Early-Stage NSCLC. J Thorac Oncol. 2020;15(1):101-109. doi:10.1016/j.jtho.2019.08.2505
7. Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol. 2017;7(5):295-301. doi:10.1016/j.prro.2017.04.014
8. Bezjak A, Paulus R, Gaspar LE, et al. Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non-Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial. J Clin Oncol. 2019;37(15):1316-1325. doi:10.1200/JCO.18.00622
9. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015;16(6):630-637. doi:10.1016/S1470-2045(15)70168-3
10. Chang JY, Mehran RJ, Feng L, et al. Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery. Lancet Oncol. 2021;22(10):1448-1457. doi:10.1016/S1470-2045(21)00401-0
11. Onishi H, Shirato H, Nagata Y, et al. Stereotactic Body Radiotherapy (SBRT) for Operable Stage I Non–Small-Cell Lung Cancer: Can SBRT Be Comparable to Surgery? International Journal of Radiation Oncology*Biology*Physics. 2011;81(5):1352-1358. doi:10.1016/j.ijrobp.2009.07.1751
12. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non–small cell lung cancer. J Thorac Cardiovasc Surg. 2010;140(2):377-386. doi:10.1016/j.jtcvs.2009.12.054
13. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled

trial. Lancet Oncol. 2019;20(4):494-503. doi: 10.1016/S1470-2045(18)30896-9
14. Nyman J, Hallqvist A, Lund JÅ, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. Radiother Oncol. 2016;121(1):1-8. doi:10.1016/j.radonc.2016.08.015
15. Timmerman RD, Hu C, Michalski J, et al. Long-term Results of RTOG 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer. International Journal of Radiation Oncology*Biology*Physics. 2014;90(1):S30. doi:10.1016/j.ijrobp.2014.05.135
16. Timmerman RD, Paulus R, Pass HI, et al. Stereotactic Body Radiation Therapy for Operable Early--Stage Lung Cancer: Findings From the NRG Oncology RTOG 0618 Trial. JAMA Oncol. 2018;4(9):1263-1266. doi:10.1001/jamaoncol.2018.1251
17. Singh AK, Gomez-Suescun JA, Stephans KL, et al. One Versus Three Fractions of Stereotactic Body Radiation Therapy for Peripheral Stage I to II Non--Small Cell Lung Cancer: A Randomized, Multi--Institution, Phase 2 Trial. Int J Radiat Oncol Biol Phys. 2019;105(4):752-759. doi:10.1016/j.ijrobp.2019.08.019
18. Videtic GMM, Hu C, Singh AK, et al. A Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer: NRG Oncology RTOG 0915 (NCCTG N0927). Int J Radiat Oncol Biol Phys. 2015;93(4):757-764. doi:10.1016/j.ijrobp.2015.07.2260
19. Kimura T, Nagata Y, Harada H, et al. Phase I study of stereotactic body radiation therapy for centrally located stage IA non-small cell lung cancer (JROSG10-1). Int J Clin Oncol. 2017;22(5):849-856. doi:10.1007/s10147-017-1125-y
20. Senthi S, Haasbeek CJA, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol. 2013;106(3):276-282. doi:10.1016/j.radonc.2013.01.004
21. Giuliani M, Mathew AS, Bahig H, et al. SUNSET: Stereotactic Radiation for Ultracentral Non-Small--Cell Lung Cancer-A Safety and Efficacy Trial. Clin Lung Cancer. 2018;19(4):e529-e532. doi:10.1016/j.cllc.2018.04.001
22. Virbel G, Le Fèvre C, Noël G, Antoni D. Stereotactic Body Radiotherapy for Patients with Lung Oligometastatic Disease: A Five-Year Systematic Review. Cancers (Basel). 2021;13(14). doi:10.3390/cancers13143623
23. Siva S, Bressel M, Mai T, et al. Single-Fraction vs Multifraction Stereotactic Ablative Body Radiotherapy for Pulmonary Oligometastases (SAFRON II): The Trans Tasman Radiation Oncology Group 13.01 Phase 2 Randomized Clinical Trial. JAMA Oncol. 2021;7(10):1476-1485. doi:10.1001/jamaoncol.2021.2939
24. Videtic GMM, Reddy CA, Woody NM, Stephans KL. Ten-Year Experience in Implementing Single-Fraction Lung SBRT for Medically Inoperable Early-Stage Lung Cancer. International Journal of Radiation Oncology*Biology*Physics. 2021;111(2):436-442. doi:10.1016/j.ijrobp.2021.05.116
25. Guckenberger M, Belka C, Bezjak A, et al. Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic: An ESTRO-ASTRO consensus statement. Radiother Oncol. 2020;146:223-229. doi:10.1016/j.radonc.2020.04.001
26. Kennedy WR, Gabani P, Nikitas J, Robinson CG, Bradley JD, Roach MC. Repeat stereotactic body radiation therapy (SBRT) for salvage of isolated local recurrence after definitive lung SBRT. Radiother Oncol. 2020;142:230-235. doi:10.1016/j.radonc.2019.08.010
27. Guckenberger M, Baus WW, Blanck O, et al. Definition and quality requirements for stereotactic radiotherapy: consensus statement from the DEGRO/DGMP Working Group Stereotactic Radiotherapy and Radiosurgery. Strahlenther Onkol. 2020;196(5):417-420. doi:10.1007/s00066-020-01603-1
28. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol. 2006;24(30):4833-4839. doi:10.1200/JCO.2006.07.5937
29. Bang A, Bezjak A. Stereotactic body radiotherapy for centrally located stage I non-small cell lung cancer. Transl Lung Cancer Res. 2019;8(1):58-69. doi:10.21037/tlcr.2018.10.07

Neutrophil-to-lymphocyte ratio as a prognostic marker in highly PD-L1 expressing advanced non-small cell lung cancer patients in first line treatment with pembrolizumab

Lídia Gomes[1,*], Samuel Pereira[1], Joana Dias[2], Ana Maria Figueiredo[1], Fernando Barata[1]

[1] Serviço de Pneumologia, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[2] Unidade de Inovação e Desenvolvimento, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
* lidiamsgomes@gmail.com

ABSTRACT

Introduction and objectives: The neutrophil-lymphocyte ratio (NLR) has been proposed to assess advanced stage non-small cell lung cancer (aNSCLC) response to immunotherapy, given the easy availability and low cost. The aim of our study was to evaluate the relationship between NLR at baseline, after the 3rd and 6th treatment cycles, and progression free survival (PFS) and overall survival (OS), in a population with aNSCLC with a PD-L1 expression ≥50% treated with pembrolizumab monotherapy in first line.
Methods: We performed a retrospective study of patients with aNSCLC with PD-L1≥50% who were treated with pembrolizumab first line from February 2017 to July 2021. NLR values at baseline and after the 3rd and 6th pembrolizumab cycles were analyzed. Optimal NLR cut-off were determined with respect to OS, by ROC curve. PFS and OS were compared by Kaplan Meyer method and Cox Proportional Hazard model for NLR measures.
Results: Sixty-six patients with PD-L1≥50% (51% males, mean age 65.8 ± 11.2 years) were included in the study. The PD-L1 expression was ≥90% in 74% of the patients. NLR≤4 after the 3rd pembrolizumab cycle were associated with a significant improvement in PFS (23.6 vs 4.3 months, p=0.002) and OS (32.9 vs 6.3 months, p=0.022), compared with NLR>4.
Discussion and conclusions: In patients with aNSCLC and a PD-L1≥50% receiving frontline pembrolizumab treatment, low NLR values after the 3rd pembrolizumab cycle were associated with significantly longer PFS and OS. This biomarker may thus help identify individuals on pembrolizumab monotherapy who are at greatest risk for disease progression.

Keywords: Lung cancer, pembrolizumab, PD-L1, neutrophil-lymphocyte ratio, Non-small Cell Lung Cancer (NSCLC)

INTRODUCTION

Lung cancer is the second most common malignancy worldwide and is responsible for the highest mortality burden [1]. In recent years, the use of Immunotherapy revolutionized the clinical practice and treatment of advanced stage non-small cell lung cancer (aNSCLC). The anti-programmed cell death protein 1 (anti-PD-1) pembrolizumab alone in first line showed a 3-year overall survival (OS) of 43.7% as opposed to an OS of 24.9% in chemotherapy-treated patients. Pembrolizumab monotherapy has become the recommended treatment for patients with aNSCLC and a programmed cell death-ligand 1 (PD-L1) tumor expression of at least 50% [2].

PD-1, also called immune checkpoint molecule, is a transmembrane protein presented in macrophages, dendritic cells and T and B lymphocytes. When the PD-1 molecule binds to one of its ligands expressed in human tumour cells (PD-L1 and PD-L2), cytotoxic T cell response is inhibited, bypassing the body's immune response against tumour cells [3,4].

PD-L1 expression has been used as a predictor of response to pembrolizumab treatment, however, variability in response to therapy has been observed regardless of the high PD-L1 expression (≥50%). This may be related to the PD-L1 antibodies variety, intra-tumour PD-L1 expression heterogeneity, and the molecular diagnostic methods used [5]. Thus, several studies have emerged trying to identify markers to predict response to immunotherapy. Peripheral markers such as the neutrophil-lymphocyte ratio (NLR) have been proposed to assess this response, given their easy availability and low cost [6-12]. In cancer, tumour associated neutrophils play as regulators of the tumour microenvironment, promoting stromal remodelling, angiogenesis, metastasis, thrombosis, and impairment of T-cell-dependent antitumor immunity [13,14]. High NLR values are associated with low survival and lower probability of response to immunotherapy in advanced stages of several types of cancer [6-8,12].

In NSCLC, high NLR prior to treatment in general has been shown to be an indicator of poor prognosis [11,15,16]. In PD-L1 ≥50% aNSCLC treated with pembrolizumab, high pre-treatment NLR has been associated with worse outcomes. Some studies have also revealed that high NLR values after a few weeks of pembrolizumab treatment can predict the response to immunotherapy and consequently the prognosis [17-19]. However, there is a highly variability of the NLR cut-off used in different studies [9,10].

We therefore performed a retrospective study to evaluate the relationship between NLR at baseline (NLR-T0), after the 3rd (NLR-C3) and 6th treatment cycles (NLR-C6), and the progression free survival (PFS) and OS, in a population with aNSCLC with a PD-L1 expression ≥ 50% treated with pembrolizumab monotherapy in first line. We also compared patients' clinical data, tumor characteristics (histology, PD-L1 expression), pembrolizumab toxicity between low and high NLR groups and its association with OS.

MATERIAL AND METHODS

We performed a retrospective study based on the analysis of data obtained from the medical records of all the patients with aNSCLC with no identification of oncogenic drivers who were treated in the Pulmonary Oncology Unit of the Centro Hospitalar e Universitário de Coimbra (CHUC), Portugal, between February 2017 and July 2021. The inclusion criteria were the patients aged more than 18 years, with diagnosis of aNSCLC accord-

ing to international guidelines, with a tumour expression of PD-L1 ≥50%, that received first line treatment with pembrolizumab in monotherapy. The exclusion criteria were prior diagnosis of other cancer, or patients previously treated for primary NSCLC. This study was approved by the Ethics Commission of Centro Hospitalar e Universitário de Coimbra.

Pembrolizumab was administered at a dose of 200mg, intravenously every 3 weeks until progression, intolerance, patient's decision to stop or for 35 cycles, as per institutional treatment protocols.

Clinical data

Clinical data concerning the patient (age, gender, ECOG Performance Status, smoking status) and their disease (histology, staging, location of the metastases when present) were extracted from electronic medical records of the patients. The data concerning the treatment and follow-up of the patients were also analysed (incidence, severity, and adverse events related to immunotherapy (iAE), disease progression or and death). Diagnosis of iAE was based on the treating healthcare practicians assessment.

Blood tests

Complete blood count with leucogram at the day of pembrolizumab initiation, after the 3rd and 6th cycles (right before 1st, 4th and 7th treatment cycles, respectively) were obtained from electronic medical records. NLR ratio were defined as absolute neutrophil count/absolute lymphocyte count.

PD-L1 expression

PD-L1 tumour expression was assessed using Dako 22C3 antibody by immunohistochemistry (IHC) in tumour samples.

Clinical endpoints

PFS was defined as the time elapsed from the date of aNSCLC diagnosis until the date of physician determined progression. Tumour progression was assessed by the Response Evaluation Criteria in Solid Tumours (RECIST) criteria version 1.1 [20]. OS was defined as the time elapsed from the date of aNSCLC diagnosis until the date of death.

Statistics

Quantitative data with a normal distribution was expressed as mean and standard deviation (SD) and data without normal distribution were expressed as median and interquartile range (P25-P75). Continuous variables differences were determined by *t*-test for normal distribution and those with non-normal distribution by nonparametric Mann-Whitney test. The χ^2 test was used to compare categorical variables. Receiver operating characteristic curves (ROC curves) were performed to analyse discrimination capability by the area under the curve (AUC), and NLR-T0, NLR-C3 and NLR-C6 optimal cut-offs were identified. Event-time distributions were evaluated using the Kaplan-Meier method and compared with log-rank test. Univariate and multivariate Cox regression analysis was used to estimate hazard ratios (HR) and corresponding 95% confidence interval (95% CI) for patients' variables and OS. A *p* value less than 0.05 was considered statistically significant. Statistical analysis was performed by using SPSS 26.0 software.

RESULTS

A total of 66 subjects with aNSCLC and a PD-L1 expression greater than 50% treated in the in Centro Hospitalar e Universitário de Coimbra with

pembrolizumab monotherapy in first line were included in this study and their characteristics are described in detail in Table 1. The mean age of participants was 65.8 ± 11.2 years and 51% were male patients. About a third of participants were never smokers. According to the histology, 65.2% patients had adenocarcinoma and 27.3% had squamous carcinoma. The PD-L1 expression was 90% or more in 74% of patients. Metastasis were present in 89.4% of the patients and 81.8% presented a performance status of 0 or 1. In all subjects, the median values of NLR-T0, NLR-C3 and NLR-C6 were 4.0 ± 4.0, 3.0 ± 3.9 and 2.6 ± 2.8, respectively.

Table 1. Patient characteristics at baseline

Patient Characteristics	Total sample (n=66)
Age at aNSCLC diagnosis, mean (SD)	65.8 (11.2)
Gender	
Male, n (%)	51 (77.3)
Female, n (%)	15 (22.7)
ECOG PS	
0-1, n (%)	54 (81.8)
2-3, n (%)	12 (18.2)
Smoking status	
Current, n (%)	41 (62.1)
Former, n (%)	5 (7.6)
Never, n (%)	20 (30.3)
Tumor histology	
Adenocarcinoma, n (%)	43 (65.2)
Squamous, n (%)	18 (27.3)
Adenosquamous, n (%)	2 (3.0)
Pleomorphic, n (%)	2 (3.0)
Bigger cells, n (%)	1 (1.5)
Initial Stage	
III, n (%)	7 (10.6)
IV, n (%)	59 (89.4)
PD-L1 expression	
≥90% n (%)	17 (25.8)
50-89% n (%)	49 (74.2)
NLR	
NLR-T0, median (IQR)	4.0 (4.0)
NLR-C3, median (IQR)	3.0 (3.9)
NLR-C6, median (IQR)	2.6 (2.8)

Toxicity to pembrolizumab occurred in 39 patients (59.1%), but treatment discontinuation was necessary in only 12 cases. Other reasons to stop pembrolizumab were disease progression, death and completed treatment in 23, 12 and 2 patients, respectively. Population mortality was 53% (n=35). Median PFS and OS in study sample were 8.9 months (95% CI 1.1-16.8) and 21.2 months (95% CI 11.7-30.4).

Concerning discriminative capacity to predict death, the ROC curve analysis showed that NLR at baseline and after the 3rd cycle provided a satisfactory (AUC 0.67, $p<0.05$) and good (AUC 0.73, $p<0.05$) performance. NLR at baseline and after the 3rd cycle provided also a satisfactory (AUC 0.68, $p<0.05$) and good (AUC 0.73, $p<0.05$) performance in predicting disease progression, respectively. NLR after the 6th cycle showed no discriminative capacity to predict death (AUC 0.69, $p>0.05$) or disease progression (AUC 0.64, $p>0.05$). Based on the ROC curve, the median value (4.0) was used as the cut-off value to classify each patient as high-NLR (more than 4.0) or low-NLR (4.0 or less) in further survival analysis.

The relation of NLR-T0 and NLR-C3 values with baseline clinicopathologic characteristics and clinical outcomes are observed in Table 2. After the 3rd cycle of pembrolizumab, patients with high NLR levels (NLR>4 vs NLR≤4) were more likely to have progression of disease and death ($p<0.05$).

At baseline, patients with low NLR levels (NLR≤4) demonstrated a longer PFS (median 21.7 vs 4.4 months, $p>0.05$) and OS (32.9 vs 11.1 months, $p>0.05$) compared with high NLR values (NLR>4), however this increase was not statistical significant. After the 3rd pembrolizumab cycle, low NLR values (NLR≤4) were associated with a significant improvement in PFS (23.6 vs 4.3 months, $p=0.002$) and OS (32.9 vs 6.3 months, $p=0.022$) compared with high NLR values (NLR>4) (Figure 1).

Table 2. Patient characteristics stratified by NLR values at baseline and after 3rd pembrolizumab cycle

Patient Characteristics	Baseline			After 3rd pembrolizumab cycle		
	NLR_T0 ≤4 N=29	NLR_T0 >4 N=36	P value	NLR_C3 ≤4 N=32	NLR_C3 >4 N=14	P value
Age at aNSCLC diagnosis, mean (SD)	64.7 (9.3)	66.5 (12.8)	>0.05	64.5 (9.6)	67.7 (11.1)	>0.05
Gender						
Male, n (%)	23 (79.3)	27 (75.0)	>0.05	27 (84.4)	8 (57.1)	>0.05
Female, n (%)	6 (20.7)	9 (25.0)		5 (15.6)	6 (42.9)	
ECOG PS						
0-1, n (%)	25 (86.2)	29 (80.6)	>0.05	29 (90.6)	12 (85.7)	>0.05
2-3, n (%)	4 (13.8)	7 (19.4)		3 (9.4)	2 (14.3)	
Smoking status						
Current, n (%)	17 (58.6)	23 (63.9)	>0.05	18 (58.6)	1 (50.0)	>0.05
Former, n (%)	11 (37.9)	9 (25.0)		13 (40.6)	5 (35.7)	
Nonsmoker, n (%)	1 (3.4)	4 (11.1)		1 (3.1)	2 (14.3)	
Tumor histology						
Adenocarcinoma, n (%)	18 (62.1)	25 (69.4)	>0.05	20 (62.5)	13 (92.9)	>0.05
Squamous, n (%)	9 (31.0)	8 (22.2)		8 (25.0)	1 (7.1)	
Others, n (%)	2 (6.9)	3 (9.7)		4 (12.5)	0	
Initial Stage						
III, n (%)	4 (13.8)	3 (8.3)	>0.05	4 (12.5)	0	>0.05
IV, n (%)	25 (86.2)	33 (91.7)		28 (87.5)	14 (100)	
PD-L1 expression						
≥90% n (%)	6 (20.7)	10 (27.8)	>0.05	9 (28.1)	2 (14.3)	>0.05
50-89% n (%)	23 (79.3)	26 (72.2)		23 (71.9)	12 (85.7)	
Adverse effect of immunotherapy (iAE)	19 (65.5)	19 (52.8)	>0.05	18 (56.3)	10 (71.4)	>0.05
Disease progression	15 (23.1)	26 (40.0)	>0.05	11 (34.4)	11 (78.6)	0.006
Mortality, n (%)	12 (44.6)	22 (55.4)	>0.05	7 (21.9)	8 (57.1)	0.038

On univariate analysis the following covariates were associated with worse OS: ECOG PS of 2 or more (HR: 3.31, 95% CI: 1.48-7.42, p=0.003) and the NLR value after the 3rd pembrolizumab cycle (HR: 3.12, 95% CI: 1.12-8.72, p=0.03). Present or past smoking habits were associated with longer OS (HR: 0.33, 95% CI: 0.12-0.86, p=0.02). On multivariate analysis the following covariates were associated with poorer OS: adverse effect of immunotherapy (iAE) (HR: 4.98, 95% CI: 1.34-18.61, p=0.017) and high NLR value after the 3rd pembrolizumab cycle (HR: 3.91, 95% CI: 1.30-11.73, p=0.015).

As in the univariate analysis, present or past smoking habits were associated with longer OS on multivariate regression (HR: 0.12, 95% CI: 0.03-0.51, p=0.005). All results are presented on Table 3.

DISCUSSION

In this observational study of patients with aNSCLC and a PD-L1 expression greater than 50% receiving frontline pembrolizumab, we showed that subjects with low NLR values after the 3rd pembrolizumab cycle had an improved PFS and OS compared with high NLR values group. After adjusting for potential confounders, we demonstrated

Figure 1. Survival curves – primary lung cancer.

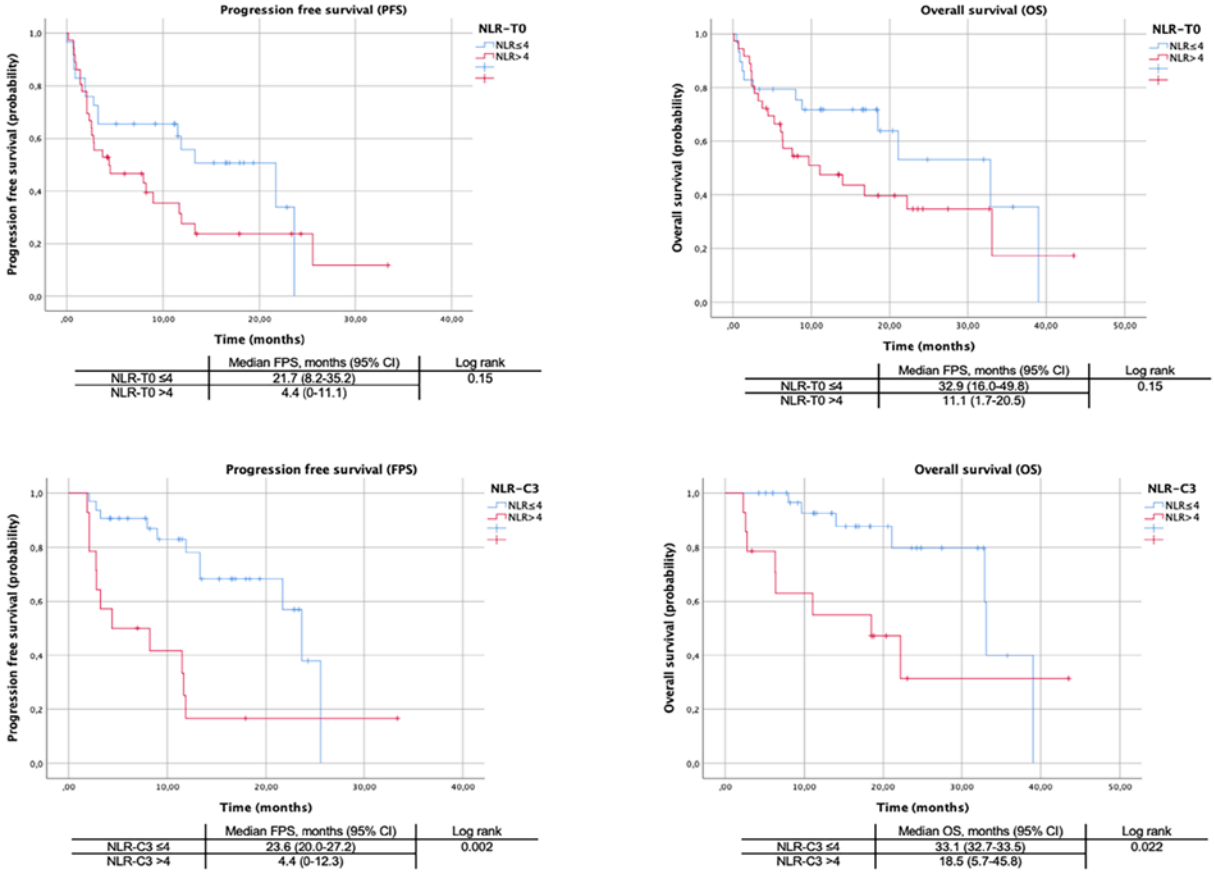


Table 3. Univariate and multivariate Cox regression analysis of OS with NLR values at baseline and after the 3rd pembrolizumab cycle

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.01 (0.98-1.05)	0.43		
Gender (male vs female)	1.63 (0.80-3.30)	0.17		
Smoking status (current/former vs never)	0.33 (0.12-0.86)	0.02	0.12 (0.03-0.51)	0.005
PD-L1 (≥90% vs <90%)	1.18 (0.54-2.58)	0.67		
ECOG PS (≥2 vs <2)	3.31 (1.48-7.42)	0.003	5.33 (0.91-31.13)	0.06
Adverse effect of immunotherapy (iAE) (present vs none)	1.83 (0.90-3.72)	0.09	4.98 (1.34-18.61)	0.017
NLR_T0 (>4 vs ≤4)	1.67 (0.82-3.38)	0.16		
NLR_C3 (>4 vs ≤4)	3.12 (1.12-8.72)	0.03	3.91 (1.30-11.73)	0.015

that NLR values >4 after the 3rd pembrolizumab cycle had almost 4-fold greater risk of death (all-cause mortality) (HR: 3.91, 95% CI: 1.30-11.73, p=0.015), compared with patients with NLR values less than 4. There was no difference in PFS and OS between high and low NLR levels at baseline and after 6th pembrolizumab cycle.

Although several studies have shown that high baseline NLR values are associated with worse PFS and OS outcomes in first line pembrolizumab treatment, there are fewer studies evaluating the importance of high NLR values during treatment. In our study we demonstrated the differences of OS and PFS in patients with high NLR values vs. low NLR values after a few treatment cycles. Similarly, Ayers *et al*. showed that an increase in the NLR between baseline and 2-8 weeks or 4-14 weeks after immunotherapy showed modestly significant correlation with lack of response in aNSCLC [19]. They further observed that sustained high NLR after initiation of treatment had a more profound impact on survival than baseline NLR, regardless of PD-L1 status. One meta-analysis showed that elevated blood NLR pre- and post-treatment was associated with significantly shorter OS and PFS in patients with NSCLC receiving PD-1/PD-L1 inhibitors [7].

The results of our study support previous published results and have clinical implications in that a sustained high level of NLR is particularly detrimental to patient outcomes and may help identify individuals who are at greatest risk for disease progression on pembrolizumab monotherapy prior to radiological assessment. Because this biomarker is readily available as part of the routine blood analysis of patients with cancer, application in the clinical practice would be easy and there would be no additional costs. Moreover, radiographic evaluation of treatment responses can be heterogeneous in immunotherapy, and atypical treatment response patterns termed pseudoprogression have been observed. Thus, blood markers after the 3rd pembrolizumab cycle (around 9 weeks after treatment initiation) may further assist in clarifying patient status for situations in which the radiologic findings are inconclusive [21].

The elevation of neutrophil values and consequently the NLR values after a few cycles of immunotherapy seems to reflect the levels of tumor associated neutrophils and thus the response to treatment, however the relationship between neutrophil counts of peripheral blood and tumor associated neutrophils is unclear.

We also demonstrated that presence of current or past smoke habits were associated with longer OS (HR: 0.33, 95% CI: 0.12-0.86, p=0.02). This finding was consistent with a previous meta-analysis that showed that either immunotherapy alone or in association with chemotherapy was less effective in never smokers, and with a recent study with first line pembrolizumab monotherapy in aNSCLC that reported consistently longer OS in current or former smokers [22,23]. This might be due to the high tumor mutational burden in patients with smoke habits compared with nonsmokers in subjects with lung cancer, which may make smoking induced lung cancer more sensitive to immunotherapy [22,24].

This study has some limitations that need to be considered. It was a single center experience with a retrospective observational design and with a limited sample size. In a future prospective study, the sample size should be calculated to detect an expected difference at the time of planning.

CONCLUSIONS

In conclusion, in patients with aNSCLC and a PD-L1 expression greater than 50% receiving frontline pembrolizumab treatment, low NLR values after the 3rd pembrolizumab cycle were asso-

ciated with significantly longer PFS and OS. This biomarker may thus help identify individuals on pembrolizumab monotherapy who are at greatest risk for disease progression.

ORCID

Lídia Gomes 0000-0002-6363-5463
Samuel Pereira 0000-0001-8341-1160
Joana Dias 0000-0002-6545-8376
Ana Maria Figueiredo 0000-0002-7949-8440
Fernando Barata 0000-0002-6306-0938

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49. https://doi.org/10.3322/caac.21660
2. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol 2019;37:537-46. https://doi.org/10.1200/JCO.18.00149
3. Rafei H, El-Bahesh E, Finianos A, Nassereddine S, Tabbara I. Immune-based Therapies for Non-small Cell Lung Cancer. Anticancer Res 2017;37:377-87. https://doi.org/10.21873/anticanres.11330
4. Wherry EJ. T cell exhaustion. Nat Immunol 2011;12:492-9. https://doi.org/10.1038/ni.2035
5. Takada K, Toyokawa G, Shoji F, Okamoto T, Maehara Y. The Significance of the PD-L1 Expression in Non-Small-Cell Lung Cancer: Trenchant Double Swords as Predictive and Prognostic Markers. Clin Lung Cancer 2018;19:120-9. https://doi.org/10.1016/j.cllc.2017.10.014
6. Li M, Spakowicz D, Burkart J, Patel S, Husain M, He K, et al. Change in neutrophil to lymphocyte ratio during immunotherapy treatment is a non-linear predictor of patient outcomes in advanced cancers. J Cancer Res Clin Oncol 2019;145:2541-6. https://doi.org/10.1007/s00432-019-02982-4
7. Jiang T, Bai Y, Zhou F, Li W, Gao G, Su C, et al. Clinical value of neutrophil-to-lymphocyte ratio in patients with non-small-cell lung cancer treated with PD-1/PD-L1 inhibitors. Lung Cancer 2019;130:76-83. https://doi.org/10.1016/j.lungcan.2019.02.009
8. Valero C, Pardo L, Lopez M, Garcia J, Camacho M, Quer M, et al. Pretreatment count of peripheral neutrophils, monocytes, and lymphocytes as independent prognostic factor in patients with head and neck cancer. Head Neck 2017;39:219-26. https://doi.org/10.1002/hed.24561
9. MacDougall K, Niazi MRK, Hosry J, Homsy S, Bershadskiy A. The Prognostic Significance of Peripheral Blood Biomarkers in Patients With Advanced Non-Small Cell Lung Cancer Treated With Pembrolizumab: A Clinical Study. Oncology (Williston Park) 2022;36:156-61. https://doi.org/10.46883/25920954
10. Ksienski D, Wai ES, Alex D, Croteau NS, Freeman AT, Chan A, et al. Prognostic significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for advanced non-small cell lung cancer patients with high PD-L1 tumor expression receiving pembrolizumab. Transl Lung Cancer Res 2021;10:355-67. https://doi.org/10.21037/tlcr-20-541
11. Takada K, Takamori S, Yoneshima Y, Tanaka K, Okamoto I, Shimokawa M, et al. Serum markers associated with treatment response and survival in non-small cell lung cancer patients treated with anti-PD-1 therapy. Lung Cancer 2020;145:18-26. https://doi.org/10.1016/j.lungcan.2020.04.034
12. Shaul ME, Fridlender ZG. Tumour-associated neutrophils in patients with cancer. Nat Rev Clin Oncol 2019;16:601-20. https://doi.org/10.1038/s41571-019-0222-4
13. Jaillon S, Ponzetta A, Di Mitri D, Santoni A, Bonecchi R, Mantovani A. Neutrophil diversity and plasticity in tumour progression and therapy. Nat Rev Cancer 2020;20:485-503. https://doi.org/10.1038/s41568-020-0281-y
14. Faget J, Peters S, Quantin X, Meylan E, Bonnefoy N. Neutrophils in the era of immune checkpoint blockade. J Immunother Cancer 2021;9. https://doi.org/10.1136/jitc-2020-002242

15. Kacan T, Babacan NA, Seker M, Yucel B, Bahceci A, Eren AA, et al. Could the neutrophil to lymphocyte ratio be a poor prognostic factor for non small cell lung cancers? Asian Pac J Cancer Prev 2014;15:2089-94. https://doi.org/10.7314/apjcp.2014.15.5.2089
16. Kazandjian D, Gong Y, Keegan P, Pazdur R, Blumenthal GM. Prognostic Value of the Lung Immune Prognostic Index for Patients Treated for Metastatic Non-Small Cell Lung Cancer. JAMA Oncol 2019;5:1481-5. https://doi.org/10.1001/jamaoncol.2019.1747
17. Kubo S, Kobayashi N, Somekawa K, Hirata M, Kamimaki C, Aiko H, et al. Identification of Biomarkers for Non-small-cell Lung Cancer Patients Treated With an Immune Checkpoint Inhibitor. Anticancer Res 2020;40:3889-96. https://doi.org/10.21873/anticanres.14379
18. Egami S, Kawazoe H, Hashimoto H, Uozumi R, Arami T, Sakiyama N, et al. Peripheral blood biomarkers predict immune-related adverse events in non-small cell lung cancer patients treated with pembrolizumab: a multicenter retrospective study. J Cancer 2021;12:2105-12. https://doi.org/10.7150/jca.53242
19. Ayers KL, Ma M, Debussche G, Corrigan D, McCafferty J, Lee K, et al. A composite biomarker of neutrophil-lymphocyte ratio and hemoglobin level correlates with clinical response to PD-1 and PD-L1 inhibitors in advanced non-small cell lung cancers. BMC Cancer 2021;21:441. https://doi.org/10.1186/s12885-021-08194-9
20. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47. https://doi.org/10.1016/j.ejca.2008.10.026
21. Beer L, Hochmair M, Prosch H. Pitfalls in the radiological response assessment of immunotherapy. Memo 2018;11:138-43. https://doi.org/10.1007/s12254-018-0389-x
22. Popat S, Liu SV, Scheuer N, Gupta A, Hsu GG, Ramagopalan SV, et al. Association Between Smoking History and Overall Survival in Patients Receiving Pembrolizumab for First-Line Treatment of Advanced Non-Small Cell Lung Cancer. JAMA Netw Open 2022;5:e2214046. https://doi.org/10.1001/jamanetworkopen.2022.14046
23. Dai L, Jin B, Liu T, Chen J, Li G, Dang J. The effect of smoking status on efficacy of immune checkpoint inhibitors in metastatic non-small cell lung cancer: A systematic review and meta-analysis. EClinicalMedicine 2021;38:100990. https://doi.org/10.1016/j.eclinm.2021.100990
24. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21. https://doi.org/10.1038/nature12477

Osimertinib-induced cutaneous vasculitis: A case report and review of the literature

Vasculite cutânea associada ao osimertinib: Relato de caso e revisão da literatura

Inês Hilário Soldin[1,*], Filipa Barros Alves[2], Joana Cordeiro e Cunha[3], Joana Santos[4], Fernanda Estevinho[5]

[1] Interna de Formação Específica em Oncologia Médica, Instituto Português de Oncologia do Porto.
[2] Interna de Formação Específica de Endocrinologia do Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos.
[3] Assistente Hospitalar de Medicina Interna, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos.
[4] Interna de Formação Específica de Anatomia Patológica, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos.
[5] Assistente Hospitalar Graduada de Oncologia Médica, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos.
* ineshsilva@gmail.com

RESUMO

Doente de 77 anos, com adenocarcinoma pulmonar estadio IVa (cT4N3M1a) sob osimertinib 80 mg/dia. Nove dias após o início do tratamento desenvolveu lesões de púrpura palpável. A biopsia cutânea revelou vasculite leucocitoclástica. Uma revisão clínica e um estudo analítico completos permitiram excluir atingimento sistémico. O fármaco foi suspenso e a doente iniciou metilprednisolona 1mg/Kg/dia, com melhoria paulatina das lesões. Ao fim de quatro semanas, reiniciou osimertinib 40 mg/dia e desmame progressivo de prednisolona até 0.5 mg/Kg/dia sem recidiva da vasculite. Boa tolerância ao osimertinib ao fim de 5 meses de seguimento. Na primeira avaliação de resposta ao tratamento apresenta resposta parcial. Trata-se do primeiro caso de vasculite cutânea induzida pelo osimertinib descrito em Portugal e o quarto a nível mundial. É, ainda, o primeiro caso de reintrodução do fármaco em metade da dose, em associação a corticoide.

Palavras-chave: Cancro do pulmão; Osimertinib; Vasculite leucocitoclástica.

ABSTRACT

A 77-year-old patient with a history of stage IVa (cT4N3M1a) lung adenocarcinoma, treated with osimertinib 80 mg/day, developed palpable purpura nine days after starting therapy. Skin biopsy revealed leukocytoclastic vasculitis. A complete clinical and lab workup for systemic involvement was unremarkable. The patient suspended osimertinib and started on methylprednisone 1mg/Kg/day. Skin lesions gradually improved. Four weeks apart, the patient resumed

osimertinib 40 mg/day along with prednisolone in a slow taping down scheme until 0.5 mg/Kg/day, without vasculitis relapse. After five months of follow-up, there is a good tolerance and a partial response to treatment. This is the first reported case of cutaneous vasculitis induced by osimertinib described in Portugal and the fourth case reported worldwide. Furthermore, this is the first report in which the osimertinib at a dose of 40 mg daily was rechallenged along with corticosteroid therapy.

Key-words: Lung cancer; Osimertinib; Leukocytoclastic Vasculitis

INTRODUCTION

Epidermal growth factor receptor (EGFR) mutations are one of the targetable driver mutations in lung cancer. The most common sensitizing EGFR mutations are the exon 19 deletion and exon 21 L858R point mutation.[1,2] Osimertinib is a third-generation irreversible tyrosine kinase inhibitor (TKI) of EGFR that is approved for first-line treatment of metastatic EGFR-mutant non-small cell lung cancer according to FLAURA clinical trial.[1,2]

Skin rash and paronychia are the most reported cutaneous adverse events (AEs). Cutaneous vasculitis is a rare AE.[3,4]

We present a case of grade 3 leukocytoclastic cutaneous vasculitis induced by osimertinib in a patient with lung adenocarcinoma. Lesions were completely resolved after TKI suspension and starting corticosteroids. The patient restarted medication with no relapsing lesions after a five-month follow-up.

CASE DESCRIPTION

We report the case of a 77-year-old Caucasian, non-smoker woman, with a history of hypertension, atrial fibrillation and a pacemaker for bradycardia. The patient was being treated with osimertinib at 80 mg/day for a stage IVa (cT4N-3M1a) lung adenocarcinoma with EGFR exon 19 mutation. Nine days after starting osimertinib, multiple petechiae appeared on the anterior aspect of both legs. There was no history of trauma or recent change in medication. Lesions were non-blanching, painless, and neither pruritic nor hemorrhagic. In the following days, lesions evolved into palpable purpura, affecting all the extension of lower limbs (Figure 1), dorsal (Figure 2) and abdominal regions. Purpura spared palmar, plantar and mucosal surfaces, face and chest. There was no fever or other clinical or laboratory evidence of systemic vasculitis. A complete workup revealed normal renal and liver function, a blood count of 158.000 platelets/μL, a normal coagulation study, and fibrinogen dosing. There was no hemolysis. Urinalysis was negative. The antinuclear antibodies and antineutrophil cytoplasmic antibodies were negative, IgA was in reference ranges, and there was no complement consumption. There is no viral or bacterial infection detected. Cutaneous biopsy revealed leukocytoclastic vasculitis (Figure 3).

Paraneoplastic vasculitis was excluded. Lesions did not occur within (or before) the lung cancer diagnosis but during treatment with osimertinb. No other inciting factors were found.

Figure 1. palpable purpura affecting the anterior and posterior aspects of lower limbs

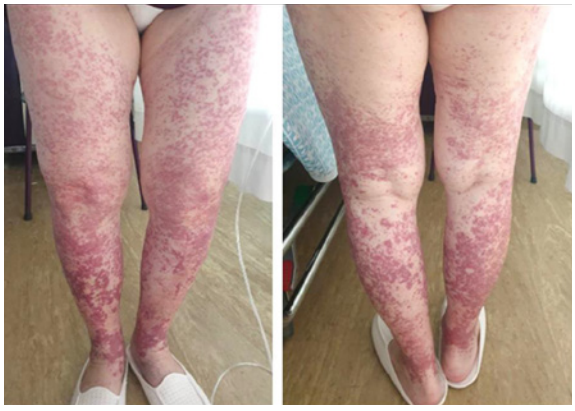
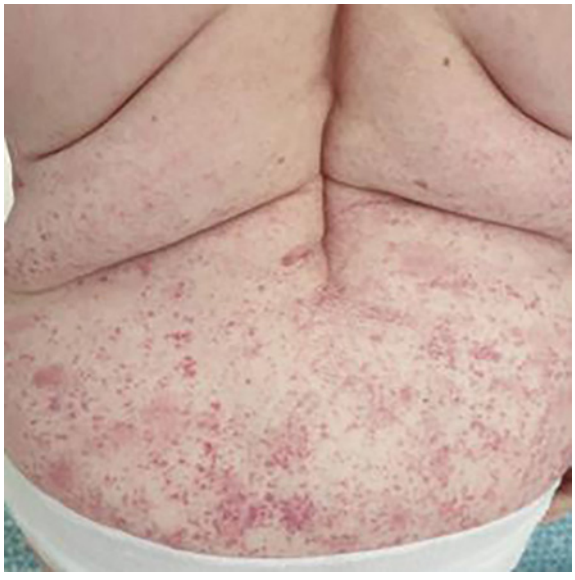
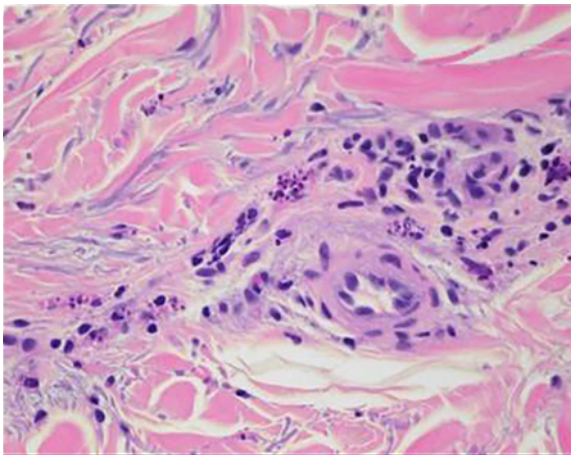


Figure 2. palpable purpura affecting the dorsal region



Therefore, the diagnosis was grade 3 osimertinib-induced leukocytoclastic vasculitis. TKI was suspended, and 1 mg/Kg/day of methylprednisolone was started. In one week, the lesions improved. After a follow-up of four weeks, medication was resumed at 40 mg/day, in association with 0.5 mg/Kg/day of prednisolone. Steroid dosing was slowly tapered off until the dose of 5 mg/day. After six weeks lesions completely resolved.

Figure 3. Leukocytoclastic vasculitis: perivascular inflammation with neutrophils and nuclear debris (HE)



After a five-month follow-up, the patient presented with partial response to osimertinib, with no vasculitis relapse.

DISCUSSION

The mechanism of osimertinib-induced vasculitis might be explained by the inflammatory response that EGFR-TKIs create on endothelial cells of cutaneous blood vessels. Vasculitis affects predominantly the lower extremities and typically spares the palmar, plantar, and mucosal surfaces.[3,4]

Iriarte C*., et al* summarized all reported cases of cutaneous vasculitis induced by EGFR-TKIs in patients with lung cancer. There were nine reported cases, of which two (including theirs) were related to osimertinib.[5,6] It is worth noting that both

are from post-marketing data. Three cases of cutaneous vasculitis were reported in the AURA, FLAURA, and ADAURA trials, but none of them were of leukocytoclastic origin.[7]

We performed a thorough review of the literature using an international database search to provide up-to-date information about Osimertinib-induced cutaneous vasculitis. Three case reports were available, one of them is a review article. All patients, including ours, were female, with ages ranging from 45 to 86 years old, and with no history of autoimmune disease. In all cases, the clinical aspect was vasculitis. The onset occurred between nine days (that is our case) to five months after initiating osimertinib. In two cases (including ours) the treatment was suspended and restarted after lesion resolution. In the case of Hamada K., *et al*, osimertinib was rechallenged at 80 mg/day with oral prednisolone (started with 25 mg/day and subsequently reduced to 7.5 mg/day).[6] The case reported by Iriarte C., *et al* is the first one reporting resolution of cutaneous vasculitis with local treatment with dapsone, without treatment interruption.[5] Lastly, the case reported by Calderon B., *et al.* is the only one describing a severe cutaneous vasculitis, with necrotic skin lesions, that progressed to systemic involvement. Osimertinib was permanently discontinued, and cyclophosphamide was started.[3] It is noteworthy that vasculitis has not relapsed in any of the cases.

Concerning our case, the decision of resuming osimertinib was based on a multidisciplinary discussion. Vasculitis clinical evolution, tumour response to osimertinib, and the available information in the literature were considered. Regarding the severity of the lesions, treatment was restarted at half-dose with corticosteroid. Local treatment was not pondered, since this a grade 3 event with major involvement of body surface area. Furthermore, there are recommendations that grade ≥2 events should lead to medication interruption for at least three weeks. Medication could be resumed after lesion improvement for grade <2.[7]

AE has not relapsed in any of the described cases, independently of the suspension of the TKI. Therefore, a dose-dependent phenomenon cannot be assumed. Alternatively, a tolerance effect to the drug may be hypothesized, as the osimertinib rechallenge at either half or full dose did not cause vasculitis.[3,5,6] Likewise, it is not possible to infer if this is early or late toxicity because the timing of developing vasculitis ranged from days to months.[3,5,6] Lastly, the pertinence of the use of systemic corticosteroids should be discussed since they could act as a confounding factor in vasculitis prognosis. More importantly, the impact of vasculitis on malignancy response to EGFR inhibitors is still controversial.[3,4,8]

Clinicians must be aware of cutaneous vasculitis as a possible, though rare, adverse event. If not diagnosed and treated on time, it can progress to systemic involvement.[6]

The scarce information available precludes any meaningful interpretation of data on osimertinib- induced cutaneous vasculitis. Further investigation is needed to characterize this AE, as well as its implications on tumor response. A complete and regular skin exam should be mandatory for all patients. Likewise, periodic assessment of tumor progression risk versus toxicity is strongly recommended.

ACKNOWLEDGMENTS

The authors would like to acknowledge Pedro Andrade, dermatologist from Hospital Pedro Hispano for his availability for performing cutaneous biopsy and patient observation and Rui Môço,

internal medicine graduated assistant from Hospital Pedro Hispano, for contributing to this clinical case discussion and management.

ORCID

Inês Hilário Soldin 0009-0008-5151-3259
Filipa Barros Alves 0009-0005-3350-2212
Joana Cordeiro e Cunha 0009-0002-6282-1587
Joana Santos 0000-0002-5551-7678
Fernanda Estevinho 0000-0002-2694-3993

REFERENCES

1. Gen, S., I. Tanaka, M. Morise, J. Koyama, Y. Kodama, A. Matsui, et al., Clinical efficacy of osimertinib in EGFR-mutant non-small cell lung cancer with distant metastasis. BMC Cancer, 2022. 22(1): p. 654.10.1186/s12885-022-09741-8
2. Lee, C.S., M. Milone, and N. Seetharamu, Osimertinib in EGFR-Mutated Lung Cancer: A Review of the Existing and Emerging Clinical Data. Onco Targets Ther, 2021. 14: p. 4579-4597.10.2147/ott.S227032
3. Calderon, B. and L. Vazquez, Severe Immune-Related Cutaneous Vasculitis Induced by Osimertinib. Arch Clin Med Case Rep, 2022. 6(4): p. 524-527.10.26502/acmcr.96550508
4. Su, B.A., W.L. Shen, S.T. Chang, L.Y. Feng, C.J. Wu, and Y.H. Feng, Successful rechallenge with reduced dose of erlotinib in a patient with lung adenocarcinoma who developed erlotinib-associated leukocytoclastic vasculitis: A case report. Oncol Lett, 2012. 3(6): p. 1280-1282.10.3892/ol.2012.647
5. Iriarte, C., J.H. Young, M.S. Rabin, and N.R. LeBoeuf, Osimertinib-Induced Cutaneous Vasculitis Responsive to Low-Dose Dapsone Without Interruption of Anticancer Therapy: A Case Report and Review of the Literature. JTO Clinical and Research Reports, 2022. 3(11).10.1016/j.jtocrr.2022.100415
6. Hamada, K., K. Oishi, T. Okita, A. Chikumoto, Y. Ohteru, K. Murakawa, et al., Cutaneous Vasculitis Induced by Osimertinib. J Thorac Oncol, 2019. 14(12): p. 2188- 2189.10.1016/j.jtho.2019.08.2507
7. AstraZeneca, TAGRISSO Highlights of Prescribing Information. 2022.
8. Fekete, G.L. and L. Fekete, Cutaneous leukocytoclastic vasculitis associated with erlotinib treatment: A case report and review of the literature. Experimental and Therapeutic Medicine, 2019. 17: p. 1128-1131.10.3892/etm.2018.6988

When the stenting in the approach to superior vena cava syndrome allows radical treatment of non-small cell lung cancer at the diagnosis

Quando o stent *na abordagem do síndrome da veia cava superior permite o tratamento radical do cancro de pulmão de não pequenas células ao diagnóstico*

Inês Hilário Soldin[1,*], Ana Luísa Nunes[2], Paulo Dias[3], Fausto Sousa[4], Fernanda Estevinho[5]

[1] Interna de Formação Específica em Oncologia Médica, Instituto Português de Oncologia do Porto.
[2] Assistente Hospitalar de Medicina Interna, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos.
[3] Assistente Hospitalar Graduado de Angiologia e Cirurgia Vascular, Centro Hospitalar de São João.
[4] Assistente Hospitalar de Radioncologia, Centro Hospitalar de São João.
[5] Assistente Hospitalar Graduada de Oncologia Médica, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos.*
ineshsilva@gmail.com

RESUMO

O síndrome da veia cava superior é uma emergência oncológica. Em 15% dos casos causa risco imediato de vida. Quando é a forma de apresentação da doença oncológica e apresenta critérios de gravidade, a abordagem diagnóstica e terapêutica multidisciplinar é desafiante e urgente. Apresentamos o caso de um doente sem diagnóstico oncológico prévio, com síndrome da veia cava superior. Apresentava edema da face, região cervical e membros superiores, dispneia e alteração do estado mental. Realizada tomografia computadorizada de tórax, que evidenciou um síndrome da veia cava superior secundário a massa mediastínica. Considerando a gravidade da obstrução, ausência de diagnóstico histológico e de metastização no restante estudo imagiológico realizado no serviço de urgência, optou-se pela colocação de *stent* endovascular de urgência, com rápida melhoria clínica. Confirmou-se o diagnóstico de adenocarcinoma pulmonar estadio IIIA. Após resposta parcial a quimioradioterapia, iniciou terapêutica de consolidação com durvalumab. Sem recidiva seis meses após o diagnóstico.

Palavras-chave: Cancro do pulmão de não pequenas células; síndrome da veia cava superior; stent endovascular; radioterapia

ABSTRACT

Superior vena cava syndrome is an oncological emergency. It is life-threatening in 15% of the cases. When it is severe and the presentation form of malignancy, a multidisciplinary diagnostic and therapeutic approach is challenging and urgent. We present the case of a patient with no previous cancer that came to the emergency department due to superior vena cava syndrome. He had oedema of the face, cervical region and upper limbs, dyspnoea and altered mental status. Chest computed tomography showed a superior vena cava syndrome secondary to a mediastinal mass. Considering the severity of the obstruction, the absence of histological diagnosis and distant metastasis, an endovascular stent was placed urgently, with rapid clinical improvement. Subsequently, we obtained a diagnosis of stage IIIA lung adenocarcinoma. After partial response to chemoradiotherapy, the patient started consolidation therapy with durvalumab. Six months after the diagnosis, there is no relapse.

Key-words: Non-small cell lung cancer; superior vena cava syndrome; endovascular stent; radiotherapy

INTRODUCTION

Superior vena cava syndrome (SVCS) results from obstruction of blood flow through the superior vena cava (SVC). An intrathoracic malignancy is responsible for 60 to 85% of the cases. Lung cancer and non-Hodgkin lymphoma are the most frequent etiologies.[1-3] SVC obstruction is the presenting symptom of a previously undiagnosed tumour in up to 60% of the patients.[1] Early symptoms include cough, dyspnea, dysphagia, dysphonia, jugular vein distention, plethora, and arm, neck and face oedema. If not promptly treated, potentially fatal respiratory distress and cerebral oedema develop.[1-3]

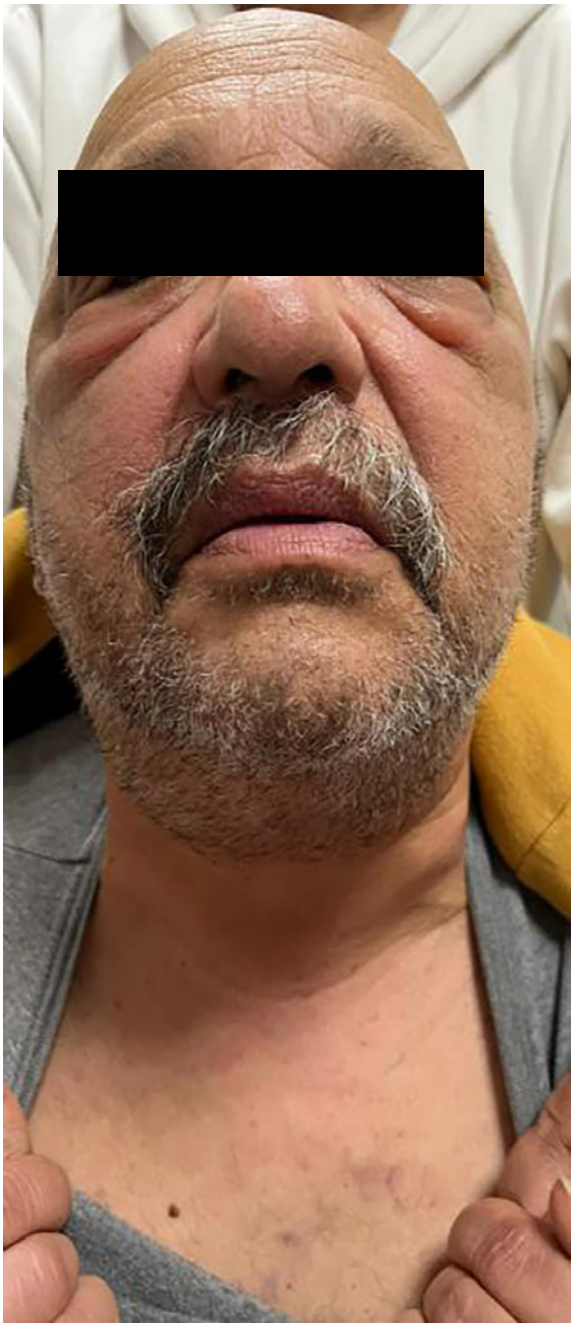
Contrast-enhanced computed tomography (CECT) is the initial diagnostic modality. The exam defines the extent of venous obstruction and collateral venous network and identifies potential thrombosis.[3] Concerning treatment, the primary goal is to alleviate symptoms. Secondary goals and intervention depend on the histology, staging and prognosis.[1,4] Treatment is guided by general recommendations since there are no evidence-based guidelines. The urgent stenting applies to severely symptomatic patients. Stenting will also be preferable when SVCS is the presentation form of an undiagnosed malignancy. Otherwise, radiotherapy (RT) could interfere with histological characterization, compromising subsequent treatment, and would not be effective in radioresistant tumours. Supportive treatment with glucocorticoids can be effective in steroid-responsive malignancies, such as lymphoma, or if the airway is compromised. However, it can hinder histological characterization. The use of diuretics is not consensual.[4-6]

CASE DESCRIPTION

Caucasian male patient, 66 years old, ex-smoker (55 pack-years), with ECOG 1 and a history of hypertension and obesity.

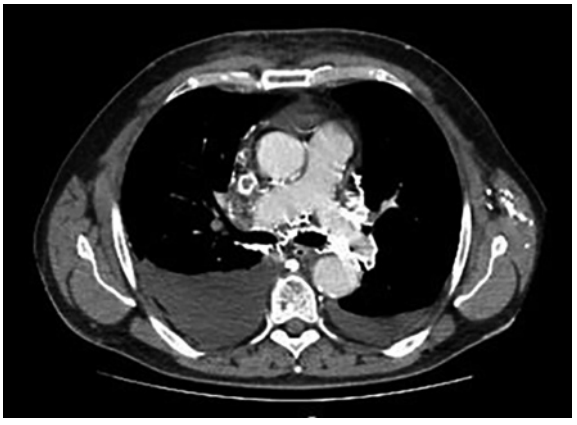
The patient presented to the emergency department due to worsening facial, neck and upper extremities oedema that started progressively for two months. Enlarged tortuous superficial bluish-

Figure 1. Facial plethora, periorbital, face and neck oedema; collateral vascular network on the chest wall



-coloured veins grew over the chest wall. He also complained of exercise dyspnoea, orthopnoea, psychomotor retardation, confusion, and sleepiness. On admission, a physical exam revealed non-pitting periorbital, face, neck and arms oedema, plethora, jugular vein distention and collateral circulation in the upper part of the trunk (Figure 1). He was hemodynamically stable, without respiratory distress or desaturation (SpO2 97%). Chest CECT scan revealed a mass with a 5,6 cm longest diameter located anteriorly to the trachea and on the right of the aorta, invading the SVC, that was almost completely obliterated (Figure 2). CT also evidenced a collateral venous network and a pleural effusion but no secondary lesions. Abdominal, pelvic and brain CECT scans excluded metastasis. Malignancy initially presenting as a grade 3 SVCS was assumed. The case was discussed by a multidisciplinary team involving medical and radiation oncology and vascular surgery physicians. Since the mass was not histologically characterized, endovascular treatment was the preferred option. Due to the severity of the

Figure 2. Obliteration of the superior vena cava, right brachiocephalic vein and proximal portion of the left brachiocephalic vein. Collateralization to the azygos system. Pleural effusion.



presentation, the procedure occurred in the first 24 hours. An angiogram was first performed demonstrating that occlusion extended from SVC to the brachiocephalic veins (Figure 2), causing extensive collateralization of azygos and hemiazygos veins, and excluding associated thrombosis. An Y-shaped stent deployment was chosen: three self-expanding nitinol stents were used from the SVC to the braquiocephalic veins in a kissing (or double barrel) technique (Figure 3). Due to the severity of SVC obstruction and the risk of stent thrombosis, the patient started low-molecular--weight heparin. In the first 24 hours, oedema has substantially diminished. Dyspnoea and orthopnoea improved in a few days.

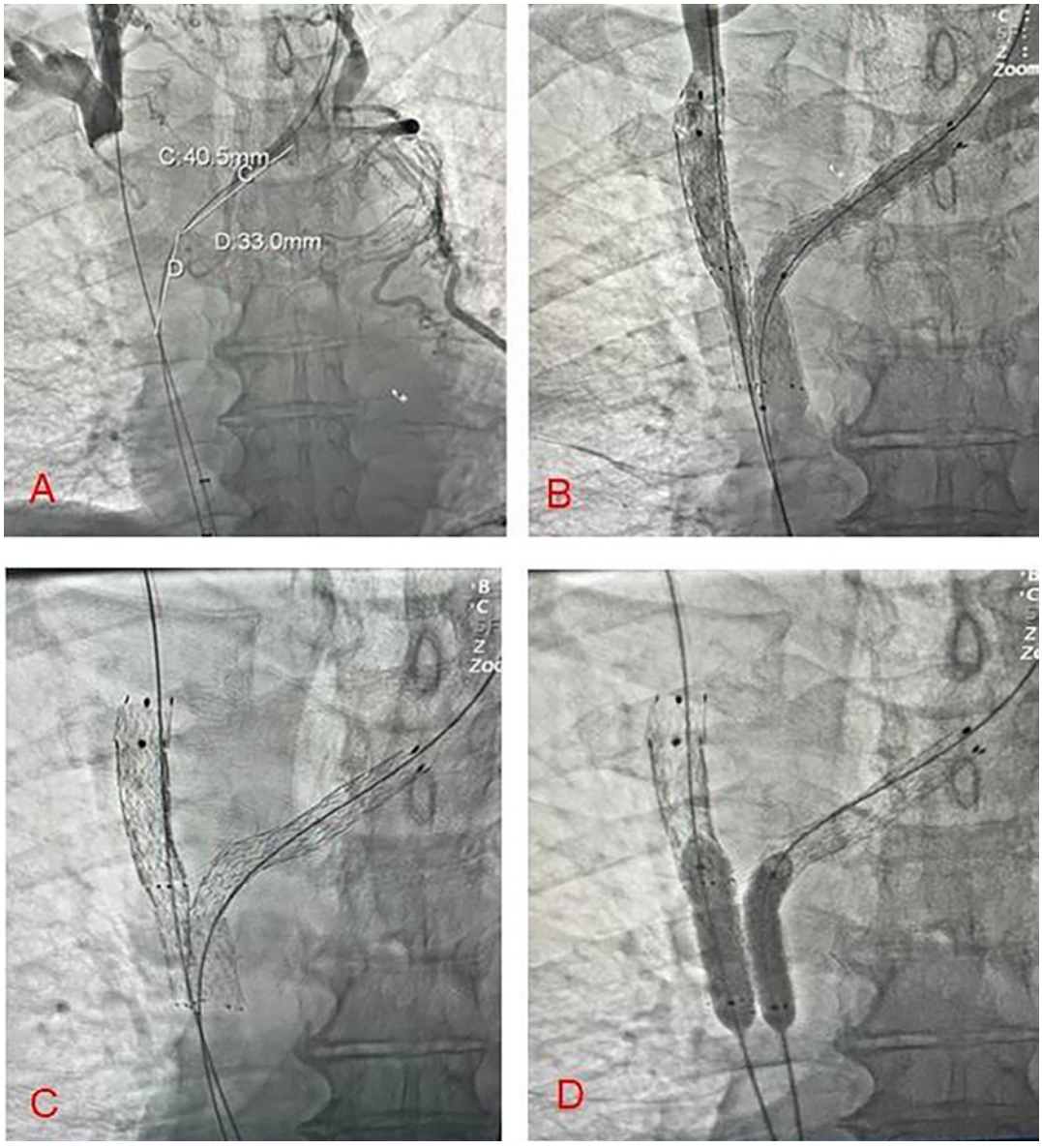
Posteriorly, an endobronchial ultrasound-guided transbronchial needle aspiration established the diagnosis of lung adenocarcinoma with PD-L1 expression of 15-20%. Next Generation Sequencing did not identify clinically significant mutations. Pleural effusion citology was negative for malignant cells. Normal positron-emission tomography completed staging. Cancer was staged as cT4N0M0 (stage IIIA). As a treatment, the patient received five cycles of radiosensitizing weekly chemotherapy with carboplatin and paclitaxel (full-dose), performed along with daily radiotherapy with curative intent (total dose of 66Gy/33fr, by photon therapy and volumetric modulated arc therapy). He obtained a partial response as the treatment's best response. After chemoradiation, he started durvalumab (10mg/kg Q2W) as a consolidation treatment. After six months, the patient is clinically stable, with an ECOG 1 and no relapse.

DISCUSSION

To stratify SVCS severity, Yu et al. proposed a grading system to stratify symptoms and to determine the urgency of intervention, facilitating communication between physicians. This system assesses the degree of oedema (laryngeal or cerebral) and hemodynamic status to categorize SVCS between life-threatening (grade 4), severe (grade 3), and non-life-threatening cases (grade 0-2).(7) Initial management depends on the underlying malignancy, the expected response to treatment and the severity of symptoms. A multidisciplinary team should decide the best treatment.(5) When malignancy initially presents as SVCS additional challenges have to be faced.

RT was formerly the gold standard for treating SVCS because lung cancer and lymphoma are characteristically radiosensitive. However, the efficacy of RT is about 80%, taking up to two weeks to improve symptoms. Furthermore, performing high-dose fractions (3-4Gy/day) will impede posterior chemoradiation with curative intent. Therefore, endovenous recanalization is nowadays considered the standard of care for patients with malignancy-related symptomatic SVCS. Few areas of venous disease provide a more satisfying experience for both the patient and the vascular specialist. Relief from severe, frequently incapacitating symptoms of venous congestion of the head and neck is almost instantaneous, and benefit is generally long lasting, as reported here. Additionally, stenting has a high technical success rate (95%-100%), efficacy rate (over 90%), as well as a low complication (less than 8%) and relapse rates (10.5% on average).[8] Besides RT, stenting does not interfere with subsequent treatment lines. Therefore, the absence of histological diagnosis determined the selected approach. In the absence of thrombosis, the decision of starting anticoagulation, which medication and duration of treatment after stenting depends on individual patient risk-benefit relationship.[3,6]

Figure 3. The extent of SVC occlusion in angiography (A); Double barrel stenting with self-expandable stents (Optimed Sinus Venous: 14x60 mm + 14x80 mm+ 14x40 mm) deployed as “kissing stents” in the SVC and both brachiocephalic veins (B, C, D).
In order to deploy stents, a left Internal jugular vein and right common femoral vein accesses were obtained, since it was not possible to cross the lesion via femoral access. Right internal jugular vein access and through-and-through (RIJV- RCFV) with GW Terumo stiff to the femoral access was used to overcome the SVC compression. Vessel was then prepared and a pre-dilatation with 10x40 mm balloon was performed. After stenting, a 10x80 balloon was used to redilate vessel. Final angiogram showed restored patency of both brachiocephalic veins and superior vena cava.



After stenting, our patient's treatment protocol was based on the phase III PACIFIC trial. The trial showed that consolidation durvalumab was associated with significant improvements in overall survival and progression-free survival, with manageable safety.

In conclusion, this clinical case illustrates how SVCS can be a true oncologic emergency and how essential is a multidisciplinary discussion. In this case, it allowed an endovascular approach in an urgent setting, not compromising subsequent treatment with chemoradiation and immunotherapy. Those treatments significantly improve morbidity and mortality in advanced-stage lung cancer.(4)

ORCID

Inês Hilário Soldin 0009-0008-5151-3259
Ana Luísa Nunes 0000-0002-5989-4219
Paulo Dias 0009-0009-8465-1620
Fausto Sousa 0000-0003-1756-9351
Fernanda Estevinho 0000-0002-2694-3993

REFERENCES

1. Hinton J, Cerra-Franco A, Shiue K, Shea L, Aaron V, Billows G, et al. Superior vena cava syndrome in a patient with locally advanced lung cancer with good response to definitive chemoradiation: a case report. J Med Case Rep. 2018;12(1):301.
2. Kinnard E. Superior vena cava syndrome in the cancer patient: a case study. J Adv Pract Oncol. 2012;3(6):385-7.
3. Patriarcheas V, Grammoustianou M, Ptohis N, Thanou I, Kostis M, Gkiozos I, et al. Malignant Superior Vena Cava Syndrome: State of the Art. Cureus. 2022;14(1):e20924.
4. Straka C, Ying J, Kong F-M, Willey CD, Kaminski J, Kim DWN. Review of evolving etiologies, implications and treatment strategies for the superior vena cava syndrome. SpringerPlus. 2016;5(1):229.
5. Azizi AH, Shafi I, Shah N, Rosenfield K, Schainfeld R, Sista A, et al. Superior Vena Cava Syndrome. JACC: Cardiovascular Interventions. 2020;13(24):2896-910.
6. Arshad AM, Pandiyan APS, Ayub, II, Chockalingam C, Thangaswamy D. Endovascular stenting for malignant superior vena cava syndrome - Case series and review of literature. Lung India. 2023;40(2):165-8.
7. Yu JB, Wilson LD, Detterbeck FC. Superior vena cava syndrome--a proposed classification system and algorithm for management. J Thorac Oncol. 2008;3(8):811-4.
8. Fagedet D, Thony F, Timsit JF, Rodiere M, Monnin-Bares V, Ferretti GR, et al. Endovascular treatment of malignant superior vena cava syndrome: results and predictive factors of clinical efficacy. Cardiovasc Intervent Radiol. 2013;36(1):140-9.

Atividades do GECP

Destaques

REUNIÃO DE OUTONO
Vieira de Leiria
Hotel Cristal Vieira Praia & Spa
13 e 14 outubro 2023

Revista GECP 2023; 1: 47-49

Reunião Outono

13 e 14 outubro 2023

Vieira de Leiria – Hotel Cristal Vieira Praia & Spa

PROGRAMA

Sexta-feira, 13 de Outubro

CURSO 1: Avaliação de Tecnologias e Outcomes Research

10h30 Avaliação clínica de Tecnologias de Saúde
Catarina Viegas Dias (NOVA-MS), Paulo Faria de Sousa (NOVA-MS)
- Tipos de estudo; medição de eficácia e efetividade; qualidade da evidência; patient-reported outcomes; casos práticos; avaliação farmacoterapêutica em Portugal (HTA).

13h00 Almoço

14h00 Avaliação económica em saúde
Julian Perelman (ENSP-NOVA)
- Conceitos de economia da saúde; evolução da despesa e os seus determinantes; os desafios do SNS e do sistema de saúde; comparações internacionais.
- Tipos de estudo de avaliação económica; medição de resultados; medição de custos; medição de valor; valor e tomada de decisão; casos práticos; avaliação económica em Portugal.

CURSO 2: Ensaios Clínicos de Iniciativa do GECP
Desenho e implementação de estudos IIS, NIS e RCTs
Constança Coelho (Dir. do Lab. de Genética FMUL)

10h00 Tipos de estudos, vantagens, limitações e aplicabilidade

10h15 Planeamento de estudos

10h45 Assuntos Regulamentares

11h00 Desenho de estudos – Protocolo, CRF e ICF

11h30 Intervalo

11h45 Desenho de estudos – Protocolo, CRF e ICF

12h30 Exercícios práticos: Desenho de estudos – IIS vs NIS vs RCTs

13h00 Almoço

14h00 Implementação de um estudo 14:30 Desenho de bases de dados 15:00 Estatística e sua interpretação

16h00 Apresentação de resultados – CSR, artigo final
• Proposta de projeto a desenvolver, a apresentar e discutir futuramente

Sábado, 14 de Outubro

TEMAS QUENTES EM 2023

09h30 Mesa redonda 1: Novidades em Doença Precoce CPNPC
Moderadores: Paulo Costa (H. Braga), Fernando Martelo (H. Luz Lisboa), Sónia Silva (H. Leiria)
• Tratamento neoadjuvante e adjuvante – Telma Sequeira (IPO Lisboa)
• Condicionantes de ressecabilidade – João Eurico Reis (CHULC)
• Papel da radioterapia – Catarina Travancinha (CUF Lisboa)

11h00 Intervalo

11h30 Mesa redonda 2: Novidades no tratamento de doentes sem Alterações Genéticas Acionáveis (AGA)
Moderadores: Gabriela Fernandes (CHULN), Ana Figueiredo (CHUC)
• Primeira linha – Fernando Barata (CHUC)
• Linhas subsequentes – Fernanda Estevinho (H. Pedro Hispano)

12h30 Almoço

13h30 Assembleia Geral
Mesa redonda 3: Novidades no CPNPC com Alterações Genéticas Acionáveis
Moderadores: José Luís Costa (Ipatimup), Marta Soares (IPO Porto) Margarida Felizardo (H. Beatriz Ângelo)
• Exão 20 – Rita Gomes (CHEDV/UMTT CHVNG/E)
• KRAS – Ana Rodrigues (IPO Porto)
• HER2 – Ana Sofia Vilariça (CHULN)
• RET – Andreia Chaves (H. Fernando Fonseca)

16h00 Encerramento da reunião

NORMAS DE PUBLICAÇÃO
DA REVISTA DO GRUPO DE ESTUDOS DO CANCRO DO PULMÃO

A **Revista do GECP** aceita para publicação trabalhos (artigos originais, de revisão, de atualização, casos clínicos, cartas ao editor, comentários críticos a artigos científicos, etc.) relacionados direta ou indiretamente com tumores torácicos.

As opiniões expressas são da exclusiva responsabilidade dos autores.

A Revista do GECP é de livre acesso. Todos os artigos estão disponíveis, de forma gratuita, em gecp.pt.

A aceitação dos originais enviados para publicação é condicionada à avaliação pelo Conselho Científico da Revista. Nesta avaliação os artigos poderão ser:

a) aceites sem alterações;
h) aceites após as modificações propostas aos autores pelo Conselho Científico;
c) recusados.

Não serão aceites trabalhos já publicados ou enviados simultaneamente a outras Revistas.

Apresentação dos trabalhos – Os textos devem ser escritos em português ou inglês, com todas as páginas numeradas e enviados num ficheiro Word (não serão aceites em PDF).

Os manuscritos deverão ser referenciados, pelos próprios autores, como artigos originais, de revisão, cartas ao editor, ou outros.

Deverá ser assinalado, no Anexo I, se o texto foi ou não escrito segundo as regras do novo acordo ortográfico da língua portuguesa.

Estrutura – Sempre que possível, será adoptado o esquema seguinte:

a) Na primeira página:
   – título do trabalho em português e inglês; nome dos autores (nome próprio e apelido) com os respetivos títulos académicos e/ou profissionais; local de trabalho ou da Instituição onde foi realizado o trabalho; endereço eletrónico do primeiro autor e opcionalmente dos co-autores.
b) Na(s) página(s) seguinte(s):
   – o resumo estruturado (Introdução e objetivos; Materiais e métodos; Resultados; Discussão e conclusões) em português que não deverá ultrapassar 250 palavras para os trabalhos originais e de revisão e de 150 para os casos clínicos;
   – o resumo em inglês com características idênticas;
   – as palavras-chave, em português e inglês (3 a 10), que servirão de base à indexação do artigo, de acordo com a terminologia do Medical Sub*ject Headings* (*www.nlm.nihgov/mesh/meshhome.html).*
c) O texto que, no caso dos artigos originais, terá em geral: Introdução, Material e Métodos, Resultados, Discussão e Conclusões
d) Agradecimentos
e) Bibliografia
f) Tabelas e Figuras.

Bibliografia – As referências bibliográficas devem ser numeradas por ordem consecutiva da sua primeira citação no texto. Devem ser identificadas no texto com números árabes no formato *superscript*. No caso das Revistas, as referências devem conter: o nome do(s) autor(es) (apelido e inicial do nome próprio), o título do artigo, o nome da publicação (abreviado) em itálico e a sua identificação (ano,volume, número e páginas).

Exemplo: **Pulmão C, Revista GE. Colaboração com a Revista. *Revista GECP* 20YY; Vol. XX(9): zz-ww.**

Se o número de autores for igual ou inferior a 5 devem incluir-se todos; se for superior, incluem-se os 3 primeiros autores seguidos da abreviatura latina *et al.*

Imagens – Todas as imagens – tabelas, figuras, fotografias, gráficos, etc. – devem ser apresentadas com qualidade que permita a sua reprodução em condições de legibilidade, numeradas e acompanhadas do respetivo título e legenda explicativa. Deverá ser sinalizado o local da sua inserção no texto.

As fotografias e outras ilustrações não podem apresentar quaisquer referências que permitam a identificação dos doentes.

As Tabelas devem ser numeradas, em numeração romana, na parte superior com o correspondente título. As Figuras devem ser numeradas, com números árabes, na parte inferior com o correspondente título.

As figuras, que incluam fotografias, devem ser enviadas em ficheiro à parte no formato TIFF ou JPEG com uma resolução mínima de 300 dpi. As figuras que contenham linhas ou conjuntos de pontos devem ser gravadas com uma resolução mínima de 800 dpi.

Conflitos de interesse – Cada um dos autores, deverá indicar no Anexo I se no manuscrito existe ou não qualquer conflito de interesse.

Modificações e revisões – No caso de a aceitação do artigo ser condicionada a modificações, estas devem ser realizadas pelos autores no prazo máximo de vinte dias.

As provas tipográficas serão realizadas pela Redacção, caso os autores não indiquem o contrário. Neste caso, elas deverão ser feitas no prazo determinado pela Redacção em função das necessidades editoriais da Revista.

Separatas – Podem ser fornecidas separatas, a expensas dos autores, quando requisitadas antes da impressão.

Pedido de publicação – Os trabalhos deverão ser acompanhados de uma declaração (Anexo I), que se encontra disponível em gecp.pt, assinada por todos os autores.

Nota final – Para um mais completo esclarecimento sobre este assunto, aconselha-se a leitura das Normas de Publicação da Acta Médica Portuguesa, 2013 disponíveis em *www.actamedicaportuguesa.com* e dos Uniform Requirements for Manuscripts Submitted to Biomedical Journals acessíveis em *ICMJE.org*.

NORMAS DE PUBLICAÇÃO DA REVISTA GECP
ANEXO I

DECLARAÇÃO

Declaro que autorizo a publicação do manuscrito:

_____,

do qual sou autor ou co-autor e que o mesmo não foi submetido para publicação ou publicado noutra Revista.

Nome dos autores:

1. _____
   Conflitos de interesse: ☐ Sim* ☐ Não Assinatura _____
2. _____
   Conflitos de interesse: ☐ Sim* ☐ Não Assinatura _____
3. _____
   Conflitos de interesse: ☐ Sim* ☐ Não Assinatura _____
4. _____
   Conflitos de interesse: ☐ Sim* ☐ Não Assinatura _____
5. _____
   Conflitos de interesse: ☐ Sim* ☐ Não Assinatura _____
6. _____
   Conflitos de interesse: ☐ Sim* ☐ Não Assinatura _____

* Indicar os conflitos de interesse de cada autor: _____

_____

_____

_____

O texto foi escrito segundo as regras do novo acordo ortográfico da língua portuguesa.

☐ Sim ☐ Não