VOLUME 4 | NÚMERO 1 | FEVEREIRO 2021

REVISTA PORTUGUESA DE Oncologia

Órgão Oficial da Sociedade Portuguesa de Oncologia

SOCIEDADE PORTUGUESA DE ONCOLOGIA

Índice

ISSN 2182-8067

Propriedade
Sociedade Portuguesa de Oncologia – Voimarães Residence, Rua de S. Teotónio, Lote 3, Loja 1, 3000-377 Coimbra;
Tel.: (+351) 239 702 200; M.: (+351) 969 220 165;
E-mail: direccao@sponcologia.pt;
Website: www.sponcologia.pt

Correspondência
Editores-Chefes da Revista Portuguesa de Oncologia - Voimarães Residence, Rua de S. Teotónio, Lote 3, Loja 1, 3000-377 Coimbra; Tel.: (+351) 239 702 200; M.: (+351) 969 220 165; E-mail: revistaspo@sponcologia.pt

Submissão de artigos
Consultar o website da SPO:
www.sponcologia.pt no menu REVISTA SPO

Edição, coordenação e produção
Springer Healthcare Ibérica • Rosario Pino 14, 28020 Madrid, Espanha.

Springer Healthcare Communications

SOJESZZ300807

Regras editoriais

A **Revista Portuguesa de Oncologia**, órgão oficial da Sociedade Portuguesa de Oncologia, é uma publicação científica na área oncológica (clínica e investigação). Publica artigos originais, artigos de revisão, casos clínicos, imagens em Oncologia, estudos de farmacoeconomia, investigação em serviços de saúde, artigos especiais e cartas ao editor.

Os artigos podem ser redigidos em português ou em inglês.

Todos os artigos que não estejam de acordo com as instruções que se seguem podem ser enviados para modificação antes de serem apreciados pelo conselho editorial. Aqui você encontrará um resumo das *regras editoriais*. Por favor, para mais detalhes, consulte a página: https://www.sponcologia.pt/pt/revista-spo/

Os artigos devem ser submetidos em formato digital na plataforma presente no site da SPO ou enviados para revistaspo@sponcologia.pt ou RSPO@springer.com, acompanhados por um formulário devidamente preenchido e assinado. Os autores podem solicitar o formulário utilizando o mesmo endereço eletrónico ou baixá-lo através do site web https://www.sponcologia.pt/pt/revista-spo/.

Para a redação dos artigos os autores devem utilizar o programa Word para Windows (ou compatível), tipo de letra calibri, tamanho 11, texto justificado, avanço da primeira linha de 1,25 cm, espaçamento simples 6 pto (depois), margens das folhas: superior e inferior – 2,5 cm, esquerda e direita – 3 cm. As imagens devem ser enviadas num ficheiro adicional em formato JPEG ou TIFF com resolução de 300 dpi.

Após envio de proposta de alteração do artigo, por parte dos revisores da Revista Portuguesa de Oncologia, os autores devem enviar uma versão revista do artigo, utilizando a função de registo de alterações (*track changes*) do Word (ou compatível) **num prazo de 10 dias**.

Os textos devem ter a seguinte estrutura:

PÁGINA 1

- **Título** em português e em inglês (menos de 130 carateres com espaços) – deve ser uma descrição breve sobre o conteúdo do artigo.
- **Nome dos autores** pela seguinte ordem: nome próprio, seguido do apelido (máximo dois nomes).
- **Filiação dos Autores**.
- **Instituição, Serviço, Cidade ou País** onde foi desenvolvido o trabalho.
- **Financiamentos e conflitos de interesses**.
- **Nome, morada, telefone e e-mail do autor para correspondência**.
- **Título breve para rodapé**.

PÁGINA 2

- Título.
- Resumo em português e em inglês. Estrutura do resumo: a) Objetivos, b) Métodos, c) Resultados e d) Conclusões. Máximo 842 carateres (com espaços).
- Palavras-chave em português e em inglês. Máximo de 5 palavras-chave, de acordo com o *Index Medicus*: «Medical Subject Headings» (MeSH).

PÁGINA 3 E SEGUINTES

Artigos originais e revisões: o texto deve conter os seguintes subtítulos: a) Introdução, b) Métodos, c) Resutados, d) Discussão, e) Conclusões e f) Referências.
Máximo 25.000 carateres (com espaços).

Casos clínicos: o texto deve conter os seguintes subtítulos: a) Introdução, b) Caso clínico, c) Discussão e d) Referências.
Máximo 15.000 carateres (com espaços) e não deve exceder 8 figuras e/ou tabelas.
As legendas das figuras e das tabelas não devem ultrapassar os 98 carateres (com espaços).

Artigos especiais: o texto deve conter os seguintes subtítulos: a) Introdução, b) Métodos, c) Resultados, d) Discussão, e) Conclusões e f) Referências.
Máximo 25.000 carateres (com espaços).

Investigação em serviços de saúde: o texto deve conter os seguintes subtítulos: a) Introdução, b) Métodos, c) Resultados, d) Discussão, e) Conclusões e f) Referências.
Máximo 25.000 carateres (com espaços).

Imagens em oncologia: não devem exceder as 6 figuras.
Devem ser enviadas em formato JPEG ou TIFF – 300 dpi.
Texto explicativo não deve ultrapassar os 2.500 caracteres (com espaços).

Cartas ao editor: comentário crítico a um artigo publicado na Revista Portuguesa de Oncologia.
Máximo 4.000 carateres (com espaços).

AGRADECIMENTOS

Quando aplicável, todos os trabalhos devem conter uma secção de agradecimentos, antes das referências bibliográficas.

REFERÊNCIAS

As referências bibliográficas devem ser numeradas pela ordem de aparecimento no texto e assinaladas em *superscript*.

Conselho editorial

Revista Portuguesa de Oncologia

Órgão oficial da Sociedade Portuguesa de Oncologia

The Journal of the Portuguese Society of Oncology

Artigo especial

Registo Oncológico Nacional: passado, presente e futuro

Portuguese Cancer Registry: past, present and future

Autores:
Filipa Alves da Costa and Ana da Costa Miranda

Afiliação:
Registo Oncológico Nacional, Instituto Português de Oncologia de Lisboa. Rua Palmira Basto, Lisboa, Portugal.

Conflitos de interesse:
No funding was received for this study.
The authors declare no conflict of interests.

Autor para correspondência:
Filipa Alves da Costa;
Registo Oncológico Nacional,
Instituto Português de Oncologia
de Lisboa. Rua Palmira Basto, Lisboa, Portugal.
Tel: 00351914084869;
Email: facosta@ipolisboa.min-saude.pt

Resumo

Este artigo apresenta uma reflexão sobre a importância dos registos de cancro para o avanço do conhecimento relacionado com a epidemiologia da doença, os padrões de tratamento e o seu impacto na política de saúde. Apresenta ainda uma abordagem histórica sobre a criação dos registos de cancro em Portugal, explanando as diferenças entre os registos de base hospitalar e os registos de base populacional. Finalmente, realça ainda a importância da existência de um registo com estas características no contexto nacional e internacional.

Palavras-chave: Registos de cancro, Epidemiologia, Farmacoepidemiologia, Neoplasmas; Portugal

Abstract

This abstract presents a reflection on the importance of cancer registry to the advancement of knowledge around epidemiology of the disease, treatment patterns and impact of health policy measures. It also provides an overview of the emergence of cancer registries in Portugal, while explaining the main differences between hospital- and population-based registries. Finally, it highlights the importance of such a registry in a national and international context.

Key words: *Cancer registries, Epidemiology, Pharmacoepidemiology, Neoplasms, Portugal*

Why is epidemiology important?

Who in the world has not heard about John Snow? Probably everyone who has some education and role or responsibility in healthcare knows he was a British physician who had a determinant role in understanding the causal mechanism involved in the emergence of cholera. In the presence of an outbreak of cholera in London, Dr Snow analysed the cases geographically and by pure observation of their location and critical thinking realised that what they had in common was the proximity to the water pumps from one of the two water suppliers in the city. This made this epidemiologist come to the hypothesis: what if the cause of this unknown disease was a microorganism present in the water that would contaminate it and hence lead to these sudden severe symptoms? This was in fact one of the first landmarks of epidemiology as a science that exists to better understand disease, its causes and determinants.

When presenting this case, if we are to start by merely indicating the number of deaths in Lambert and the number of deaths in Southwark (the two regions of London illustrated above) and then ask for the respective mortality rates, the answer will be impossible. Those that understand the basis of epidemiology will immediately realise this because the existing population in each of the locations is unknown. To be able to understand the evolution of a disease, looking at case studies may be ideal and allow clinicians, researchers and even policy makers to understand the main features of an illness, the symptoms and to sometimes study uncommon previous exposures, etc. However, to characterise a disease in epidemiologic terms, the population at risk needs to be known so the main indicators are possible to extract; that is, mortality, incidence, prevalence and survival. Looking from a lay perspective, when we get diagnosed with any disease, the first questions asked are: Why did I get this disease? What were the odds of getting it? What will happen next? (i.e. will I die?) How likely is it for me to survive?

In the last 5 years, the news keep stating that the health-literacy of the Portuguese population is low and that particularly the Ministries of Health and of Education should come together to invest in raising health-related literacy. This is most commonly achieved by providing reliable information to Portuguese citizens. However, this does not guarantee, per se, that they will be able to use it correctly or even to understand it, but surely it is a starting point. So, if we want to be able to provide our population with the answers to disease-related questions, we need the mechanisms in place to understand the patterns of disease internationally and nationally, and at the regional level.

What is the difference between a hospital-based and a population-based registry?

The term Registry is a MeSh Term and is defined as 'The systems and processes involved in the establishment, support, management and operation of registers, e.g. disease registers' (National Center for Biotechnology Information, 1972). Others have described it as 'an organised system that through observational methods collects uniform data (including clinical but not exclusively), with the purpose of evaluating specific outcomes'.[1] Since the 1970s, hospital-based registries for cancer have existed in Portugal. As early as 1963, the National Institute of Statistics, under the guidance of an oncologist from the Lisbon Portuguese Oncology Institute, started to record all cases treated in this hospital. The annual aggregated analysis and publication of such cases was initiated then, which included crude estimates of cancer hospital incidence. However, real hospital registries were only created 15 years later and were distributed throughout the country; for example, the Lisbon Portuguese Institute of Oncology hospital registry was created in 1978.

A hospital-based registry has the advantage of being created to the image of the hospital, eventually even compatible with the software in use, and in general enabling very detailed information about cases diagnosed or treated at that specific institution. This type of information may be particularly useful for clinicians to explore patterns of treatment within their teams and for hospital administrators to extract indicators that may provide important clues on the quality of care (e.g. time elapsed from diagnosis to treatment intitution). Also, because it is limited in the size and infrastructure involved, the frequency of updating the information contained may be quite intense. The disadvantage is that it is of limited use for epidemiology purposes because the population at risk is unknown. This has always been true, but gained additional relevance with the emergence of the law issued in 2016 that allows free circulation of patients within the National Health Service (Dispatch 5911-B/2016, issued on 3 May 2016 - Diário da República, 2.ª série — N.º 85). There have been various studies developed resorting to hospital-based registries, and reading some of these will perhaps allow a better understanding of their utility. We refer specifically to three examples: the first two are extremely useful to understand the aetiology and determinants of specific cancers. Tuyns explored in depth the effect of alcohol on cancer of the larynx and the cumulative effect of alcohol and tobacco.[2,3] Falcão et al. explored the effect of long-term continuous exposure to wine on the development of gastric cancer.[4] The third study details the quality of care provided to terminal patients, analysing the treatments they were submitted to during the last 3 months of their lives.[5]

Conversely, population-based registries include information on the population covered – a characteristic that makes them extremely useful as a source for producing varied epidemiology estimates. These registries may be used for: 1) gathering information on new cases and consequently study and issue periodic data on incidence, mortality and survival, enabling the assessment of the magnitude of cancer burden; and 2) providing data that may guide health policy and monitor the impact of eventual new policies adopted.

The first population-based registry in the Portuguese territory dates back to Lourenço Marques, in Mozambique, currently known as Maputo. The first experiences in developing this registry were between 1956 and 1961, and covered a population of 100,000 inhabitants. In Portugal, the pioneer population-based registries were Viana do Castelo and Vila Nova de Gaia, created in 1976 and 1980, respectively. Later in 1988, three regional registries were created and regulated by law; the Registries of the South Region (includes the regions of Lisboa e Vale do Tejo, Alentejo, Algarve and Autonomous Region of Madeira) (Law 35/88, issued 16 January 1989, Diário da República 219, Série I); the North Region; and the Central Region – each covering 4.3, 3.6 and 2.3 million inhabitants, respectively.[6] One year later, the Regional Registry of Azores was created, covering around 247,000 inhabitants (Regional Regulatory Decree 33/89 A, issued on the 22 September 1989, Diário da República 219, Série I).

The development of the South Region Registry was a complex process, where, in an initial phase, the conceptualisation and establishment of the structure was advised by a consultant from the International Agency for Research on Cancer.

Because the population-based registry is, in fact, based on a collection of hospital-based registries for which exhaustive and rigorous information is needed and cannot be obtained in a totally automatic manner, one of the conditions advised for a successful registry is to ensure there is a medical oncologist nominated as registry coordinator in each of the institutions.

In 2017, a new decree was established anticipating the implementation of a National Cancer Registry (RON, Registo Oncológico Nacional), covering all inhabitants in Portugal; that is, 10.5 million people (Law 53/2017, issued 14 July 2017, Diário da República n.º 135/2017, Série I). When such a registry was created, a previous assessment was made on the structure and quality of the existing regional registries. It was decided that the one collecting more information and in a more robust way was the South Region; therefore this was the platform chosen to host the National Registry. Thus, during the first 2 years of implementation and progressive transition from the old system into this new one, education and training occurred throughout the country, creating capacity in the field to work with the structure imposed and the methods used. However, because it was considered essential to ensure all parts were considered equally important, and perhaps in an effort to motivate all to pursue the collaboration into this common aim of increasing the knowledge of cancer and its treatment, it was always considered and foreseen in this decree that the registry would be administered by one of the three oncology institutes in rotation periods of 3 years.

The registry of new cancer cases in this national platform was therefore initiated on 1 January 2018. In parallel, it was determined that the previously identified cases by both the Central and North registries should be migrated to the national platform during the first three years (2018-2021). During 2018, the migration of cases from the Centre Registry was accomplished. However, such was not the case for the North Region, due to interoperational issues encountered. Nonetheless, the first national publication pertaining all new cases diagnosed in 2018, was issued in January 2021, as foreseen by law.[7]

Effectiveness monitoring

From the start, cancer registries have been considered a powerful tool for the characterisation of cancer, which includes detailed information not only about the disease but also about the treatments administered and the subsequent results. However, traditionally, this focus on treatment was quite superficial and was mainly based on the collection of dichotomous variables telling us if individuals had been submitted to radiotherapy, surgery, chemotherapy, other treatments or combinations of these options. Only recently, with the emergence of new treatments – which are progressively approved with increasing costs to the National Health Service and with lower levels of evidence (partly a result of the orphanisation concept) – growing interest has emerged to obtain more detailed information on the treatments administered. In fact, one of the new aims established by the law 53/2017 is the duty of the registry to monitor effectiveness. This implies that from the hospital perspective, changes in the traditional structure must be made; therefore, currently, not only is it important to have a medical oncologist coordinating the registry, but the ability for this coordinator to liaise with the other members of the healthcare team to obtain detailed information on the timing of administration, the doses administered, the occurrence of adverse drug reactions, etc., is of utmost importance. In this context, part of the change also includes ensuring that such multiprofessional teams are fully functional – in particular oncologists, nurses and pharmacists. Although poles of good practice exist where case registry is supplementary made by oncologist (disease characteristics) and pharmacist (medication characteristics, including dose administered and duration of therapy), these are still a minority suggesting cultural and organizational change is needed. Obtaining information on effectiveness is indeed extremely important, particularly in the context of the National System for Health Technology Assessment (Law 97/2015, issued 1 June 2015, Diário da República n.º 105/2015, Série I), which anticipates that every new medicine entering the market with a conditional approval must be reassessed after 2 years. Cancer medicines are currently all approved at the central level by the European Commission, and this decision is based on information gathered by the market holder, traditionally in phase 3 randomised, controlled trials. However, such trials have limitations; namely their duration, the limited sample size and often the eligibility criteria imposed on trial participants, to name a few. This implies that sometimes medicines are approved with insufficient evidence or with evidence collected on a population that does not necessarily totally match the real population. For this reason, health technology assessment (HTA) agencies have been encouraging the use of real-life data to supplement information collected in trials (also called phase 4 trials). These may be used to collect additional data on safety, on effectiveness, or on both.[8] The difficulty is, in fact, to be able to collect outcomes that are mature enough to provide useful and reliable data and that are still compatible with the demands of the regulatory world. Since the creation of this system, RON has contributed to the HTA of nivolumab and pembrolizumab for lung cancer and melanoma, and is currently monitoring the use of palbociclib in breast cancer.[9-11] Another study, focusing on safety, was also conducted analysing all treatments used for advanced melanoma.[12]

Why should we have cancer registries?

We know today that cancer is the main cause of mortality and morbidity, both in industrialised and developing countries. The reason we know this is because existing registries allow the progression of knowledge. Having registries also informs us on the detailed characterisation of illness in the population; some of the data periodically issued by national registries also include information on the most common types of cancer and on the stage that diagnosis more frequently occurs. Registries can also 1) provide very useful information for healthcare management and evidence-based implementation of policy measures; namely, to characterise and compare

between regions the time elapsed between diagnosis and the initiation of treatment, enabling, for instance, the assessment of inequalities; and 2) permit an understanding of the effects of having screening programmes implemented in the field in terms of disease staging. Finally, such data also may be used at the institutional level for benchmarking purposes, so it is possible for hospital managers to have the main indicators of their institution compared with the national average, characterising the care sought and the offer provided. This allows a benchmark experience based simply on process indicators or going as far as clinical outcomes; for example, is survival different in hospital X compared to the national average for this specific type of cancer? Indicators also may be extracted for financing purposes; again either based on performance measures (e.g. proportion of cases registered) or on clinical outcomes (at the moment absent in Portugal but potentially to be implemented in future work; e.g. survival by staging).

What data sources are connected in the Cancer Registry?

The Cancer Registry is based on record linkage that allows real-time integration of data from clinical databases. This is a disease registry, so inclusion in the database is triggered by the identification of a new cancer case. The system was initially set up in the 1990s as a simulation of a network where the information was sent to the central database using encrypted information in packages to preserve the anonymity of individuals.

In 2005, with the creation of the citizen's card, Portugal gained a competitive advantage over other European countries as this access enabled the creation of a unique patient record so a longitudinal follow-up of the individual who enters the National Health System – but may pass through different institutions – exists. At this point in time the structure of the database was changed from a purely data entry format to a mixed system, where all data previously existing in data sources could be imported into an intermediate database and the registry would then have the possibility to upload and integrate them. Currently, there is the possibility to integrate information from various sources, including the pathological laboratory (biopsy result or surgical fragment), the oncology department (first appointment or chemotherapy treatment), the operating theatre (surgical procedure) or radiotherapy department (radiotherapy treatment) (Figure 1). This huge step was essential for gaining time in the process, and it constituted a method for error minimisation. The integration of the electronic prescription system is currently underway.

As mentioned, such a system is designed to minimise errors, so a quality management system is included where inconsistencies between information are identified, allowing the minimisation of potential bias arising from the collection of data in different centres, clinical settings and departments.

Contribution of the national registry to international data sources

The South Regional Registry, which covers the widest population, has long contributed to various international studies and networks of knowledge exchange. These contributions are extremely important as they enable researchers, policy makers and even the general public to understand the differences in cancer patterns in Portugal in the European context, and even in the international context. Again, even for benchmarking purposes, such studies are valuable as hypothesis formulated

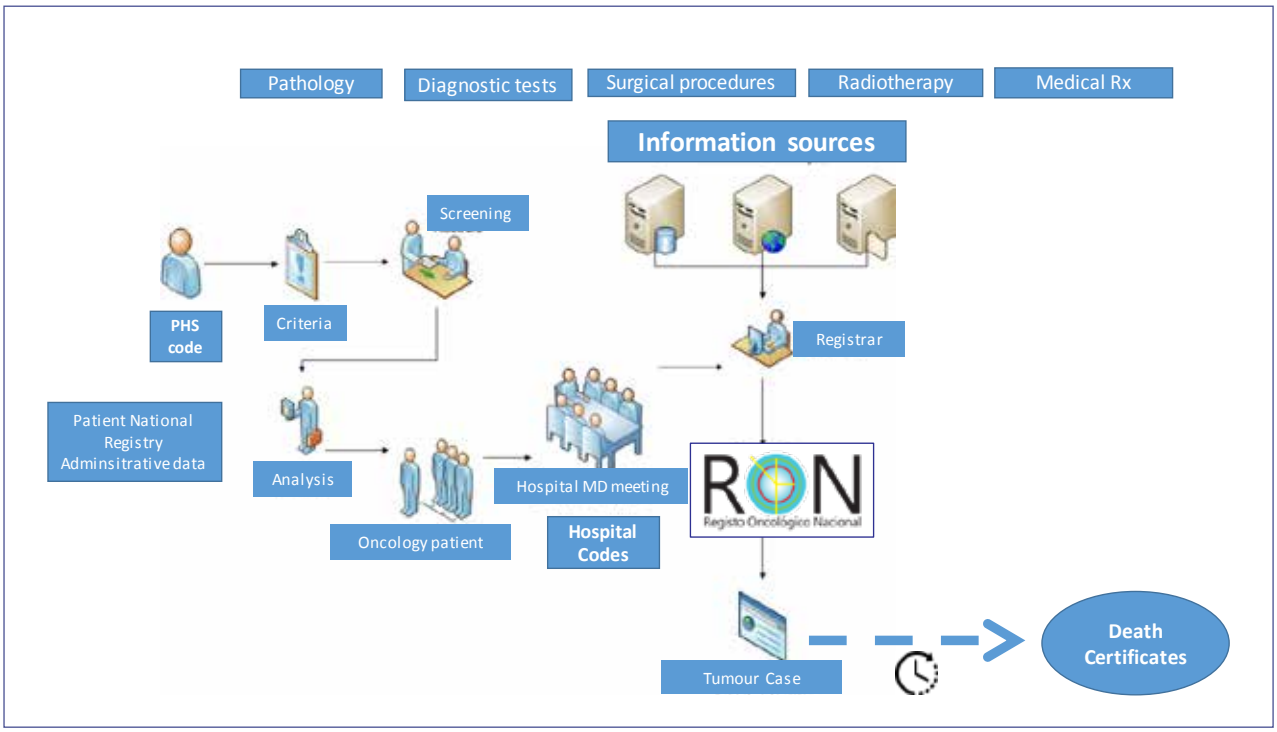


Figure 1. Structure and data sources contributing to the Portuguese Cancer Registry.

based on differences identified may impact on health policy measures to be adopted. Some of these collaborations worth highlighting, given their contribution to the advancement of knowledge, include:

- The SUDCAN collaborative study where net survival from gastric cancer was compared between six European Latin countries (Belgium, France, Italy, Portugal, Spain and Switzerland).[13]
- Various studies conducted in collaboration with the Association for Cancer Registration and Epidemiology in Romance language countries (GRELL), exploring the differences in biomarkers testing for breast cancer.[14]
- In collaboration with 61 other countries, Portugal also participated in the Automated Childhood Cancer Information System (ACCIS), where geographical differences were identified in the incidence of children's and adolescents' tumours.[15]
- A study on rare cancers undertaken in collaboration with other nine European countries where the contribution of occupation risk factors to the development of uveal melanoma was explored.[16]
- A study conducted with several European countries and the United States aiming to compare surgical and radiation treatment for elderly women with early-stage breast cancer, showing significant international differences.[17]
- A study comparing colorectal incidence and mortality across 21 European countries and discussing their links with screening practices.[18]

Conclusions

Population-based cancer registries are indispensable tools for planning healthcare provision and for evaluating the performance of the National Healthcare System in the oncology context. Currently, given the structure and organisation of the National Cancer Registry, it assumes a decisive importance in the evaluation of new molecules in a real-world context. To achieve the full potential of a National Cancer Registry, it is essential that all oncologists and researchers actively contribute to ensure comprehensive registry data.

Acknowledgements

The authors acknowledge the enormous contribution of all the network, including collaborators of all hospital and healthcare units throughout the country. We also acknowledge the special contribution of the research team within the central structure.

Funding

No funding or sponsorship was received for this study or the publication of this article.

Conflict of interests

Ana da Costa Miranda declares no conflict of interests. Filipa Alves da Costa reports having received congress registration fees from Roche Farmacêutica SA.

Compliance with ethical principles

This manuscript is based on the ideas and experiences of the authors and does not therefore require any ethical approval. In some parts of the manuscript, we refer to studies undertaken in humans previously developed in the context of the normal functions of the Registry, and as mandated by law; hence, ethical approval is not required.

References

1. Gliklich R, Dreyer N. Registries for Evaluating Patient Outcomes: A User's Guide. Rockville, MD: Agency for Healthcare Research and Quality. AHRQ Publication No. 10-EHC049: 2010.
2. Tuyns AJ. Association of tobacco and alcohol in cancer. Bull Schweiz Akad Med Wiss. 1979a;35(1-3):151-158. In French.
3. Tuyns AJ. Epidemiology of alcohol and cancer. Cancer Res. 1979b;39(7 Pt 2):2840-2843.
4. Falcão JM, Dias JA, Miranda AC, et al. Red wine consumption and gastric cancer in Portugal: a case-control study. Eur J Canc Prev. 1994;3(3):269-276.
5. Braga S, Miranda A, Fonseca R, et al. The aggressiveness of cancer care in the last three months of life: a retrospective single centre analysis. Psycho-Oncology. 2007;16(9):863-868.
6. Instituto Nacional de Estatística, I.P. Estatísticas Demográficas 2019. Lisboa, 2020. ISBN 978-989-25-0535-0
7. Miranda AC, Mayer-da-Silva A, Glória L, Brito C. Registo Oncológico Nacional de todos os Tumores na População Residente em Portugal e 2018. Lisboa, Jan 2021. Ed Registo Onológico Nacional. ISBN: 978-989-95280-3-0.
8. Paris V, Slawomirski L, Colbert A, et al. In: Gautam A, editor. New Health Technologies Managing Access, Value and Sustainability. Paris: OECD Publishing; 2017.
9. Borges FC, Murteira R, Mendes GP, et al, on behalf of the RON network. Monitoring real-life utilization of pembrolizumab in advanced melanoma using the Portuguese National Cancer Registry. Pharmacoepidemiol Drug Saf. 2020;30(3): 342-349.
10. Murteira R, Borges FC, Mendes GP, et al, on behalf of the RON network. Real-world effectiveness of pembrolizumab in previously treated non-small cell lung cancer: a population-based cohort study. Pharmacoepidemiol Drug Saf. 2020;29(10):1295-1302.
11. Costa FA, Ramos C, Murteira R, et al. The Cancer Registry as an ally in monitoring treatment effectiveness. Pulmonology. 2019;25(1):3-8.
12. Aguiar JP, Borges FB, Murteira R, et al. Using a cancer registry to capture signals of adverse events following immune and targeted therapy for melanoma. Int J Clin Pharm. 2018;40(4):852-861.

13. Glória L, Bossard N, Bouvier A-M, et al. Trends in net survival from stomach cancer in six European Latin countries. Eur J Canc Prev. 2017;26:S32-S39.

14. Crocetti E, Caldarella A, Ferretti S, et al. Consistency and inconsistency in testing biomarkers in breast cancer. A GRELL study in cut-off variability in the Romance language countries. Breast. 2013;22(4):476-481.

15. Steliarova-Foucher E, Kaatsch P, Lacour B, et al. Quality, comparability and methods of analysis of data on childhood cancer in Europe (1978–1997): Report from the Automated Childhood Cancer Information System project. Eur J Canc. 2006;42(13):1915-1951.

16. Lutz JM, Cree I, Sabroe S, et al. Occupational risks for uveal melanoma results from a case-control study in nine European countries. Canc Causes Contr. 2005;16(4):437-447.

17. Kiderlen M, Bastiaannet E, Walsh PM, et al. Surgical treatment of early stage breast cancer in elderly: an international comparison. Breast Cancer Res Treat. 2012;132(2):675-682.

18. Cardoso R. et al. Divergent trends in colorectal cancer incidence, mortality and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. The Lancet Oncology. Accepted for publication.

Portaria 35/88, 16 January, Diário da República 13/1988, Série I, 16/01/1988
Decreto-Regulamentar Regional 33/89-A, Diário da República 219, Série I, 22/09/1989
Lei 53/2017, Diário da República 135/2017, Série I, 14/07/2017
Dec-Lei 97/2015, issued 1 June, Diário da República n.º 105/2015, Série I de 2015-06-01

Artigo de revisão

Síndromes hereditárias raras: O Complexo de Carney

Rare hereditary syndromes: Carney Complex

Autores:
Pedro Valente[1]
Leonor Gomes[2]

Afiliação:
[1]Interno de Formação Específica em Cirurgia Geral da Unidade Local de Saúde de Matosinhos (ULSM)

[2]Assistente Hospitalar Graduada do Serviço de Endocrinologia, Diabetes e Metabolismo do Centro Hospitalar da Universidade de Coimbra (CHUC)
Professora Doutora, Regente da Cadeira de Endocrinologia da Faculdade de Medicina da Universidade de Coimbra

Conflitos de interesse:
Sem conflitos de interesse

Autor para correspondência:
Pedro Valente
Travessa Senhor de Matosinhos, 86,
Santa Marinha
4400-305 Vila nova de Gaia
Portugal
Email: pedrovalente90@hotmail.com

Resumo

Introdução: O Complexo de Carney (CNC) é uma síndrome endócrina múltipla rara de transmissão autossómica dominante, composta por neoplasias cutâneas, cardíacas, neuronais e em várias glândulas endócrinas. Está associada a mutações inativadoras do gene codificador da subunidade reguladora tipo 1 alfa, da proteína cinase A (PRKAR1A).

Objectivo: Revisão científica sobre o CNC.

Métodos: Pesquisa nas bases de dados da *PubMed* e *b-on*, de literatura científica sobre cada uma das componentes da doença, alterações genéticas e recomendações de seguimento.

Revisão: O Complexo de Carney apresenta como manifestações mais frequentes alterações da pigmentação cutânea, mixomas cutâneos ou cardíacos e síndrome de Cushing por doença adrenocortical nodular pigmentar primária. Alterações da função tiróidea e hipofisária, bem como o aparecimento de tumores testiculares e ováricos são outros exemplos da hiperactividade endócrina inerente à síndrome. A distinção face a outras síndromes com manifestações cutâneas e endócrinas pode ser difícil. Em termos genéticos, a maior parte destes doentes apresenta mutações inactivadoras no gene PRKAR1A que codifica a subunidade reguladora tipo 1 alfa da proteína cinase A (PKA). A função anormal da proteína cinase A resulta em alterações na transcrição celular, metabolismo, progressão do ciclo celular e apoptose, contribuindo para o processo de tumorigénese. Uma vigilância dirigida às diversas manifestações da doença deve ser feita de forma frequente nestes doentes.

Conclusão: Apesar da heterogeneidade genética e clínica, os critérios de diagnóstico do CNC encontram-se hoje bem definidos, possibilitando um diagnóstico e abordagem mais precoces das componentes da doença, bem como uma orientação e acompanhamento familiar mais adequados.

Palavras-chave: Complexo de Carney, PRKAR1A, Lentiginose, Mixoma, Doença Nodular Pigmentada Primária da Supra-Renal (PPNAD).

Abstract

Introduction: *Carney Complex (CNC) is a rare multiple endocrine syndrome following an autosomal dominant inheritance pattern, compound by skin, cardiac, neuronal and endocrine neoplasia. It's associated to inactivating mutations in the protein kinase A regulatory subunit type 1α(RIa) gene (PRKAR1A).*

Objective: *CNC scientific revision.*

Methods: *Research in* PubMed *and* b-on *databases of scientific literature regarding each of the disease components, genetic alterations and follow up recommendations.*

Revision: *CNC presents as most frequent manifestations skin pigmentation changes, skin or cardiac myxoma and Cushing's syndrome by primary pigmented nodular adrenocortical disease. Alterations in pituitary and thyroid function, as well as the appearance of ovarian and testicular tumors are other examples of endocrine hyperactivity inherent to this syndrome. To differentiate from other syndromes with cutaneous and endocrine manifestations can be difficult. In genetic terms, the majority of these patients show inactivating mutations in the PRKAR1A gene which codes for the regulatory subunit type 1α (RIa) of the protein kinase A. The abnormal function of the protein kinase A results in changes in cellular transcription, metabolism, cell cycle progression and apoptosis, contributing to the tumorigenesis process. Surveillance directed at different manifestations of the disease should be performed frequently in these patients.*

Conclusions: *Although the clinical and genetic heterogeneity, the CNC diagnosis criteria are now well established, enabling an earlier diagnosis and approach to the disease components as well as more suitable familiar orientation and monitoring.*

Keywords: *Carney Complex, PRKAR1A, Lentiginosis, Myxoma, Primary Pigmented Nodular Adrenocortical Disease (PPNAD).*

Introdução

O Complexo de Carney (CNC) foi pela primeira vez descrito em 1985 por James Aidan Carney como o complexo dos mixomas, das manchas cutâneas pigmentadas e da hiperactividade endócrina[1]. Designações anteriores para o CNC podem ser encontradas, nomeadamente a síndrome NAME (nevos, mixomas auriculares, neurofibroma mixóide e efélides) descrita em 1980 por Atherton *et al*[2] e a síndrome LAMB (pigmentação cutânea lentiginosa, mixoma auricular, mixoma mucocutâneo e nevos azuis) por Rhodes *et al* em 1983[3]. Salienta-se que o termo "tríade de Carney" corresponde a uma entidade completamente distinta, que inclui leiomiossarcoma gástrico, condroma pulmonar e paraganglioma extra-adrenal[4,5,6].

Carney constatou, numa população de 40 indivíduos, a coexistência de determinadas doenças raras cuja improbabilidade de ocorrerem simultaneamente sugeria uma síndrome única[1]. Posteriormente, vários casos descritos em indivíduos aparentados evidenciaram a associação das patologias referidas por Carney, reforçando o carácter hereditário desta síndrome autossómica dominante[4].

O CNC é definido pela associação de múltiplas neoplasias endócrinas e manifestações essencialmente cardíacas e cutâneas[5]. As últimas são as mais comuns, maioritariamente sob a forma de lentiginose facial e da mucosa genital[6-10]. Os mixomas cardíacos são a segunda componente mais frequente e o seu diagnóstico precoce é fundamental, pois as complicações cardioembólicas constituem a principal causa de morte nestes doentes. Das neoplasias endócrinas destacam-se a doença adrenocortical nodular pigmentada primária (PPNAD), adenomas hipofisários produtores de somatotrofina (GH) ou prolactina, adenomas ou carcinomas tiroideus, neoplasias testiculares (tumores de células de Sertoli calcificantes variante de grandes células - LSSCST) e quistos ou carcinomas do ovário. Menos frequentes são os schwanomas melanóticos psamomatosos (PMS), adenomas dos ductos mamários e osteocondromixomas[5-9,11]. Algumas manifestações são mais específicas deste complexo como a PPNAD, enquanto outras são menos, como os nódulos tiroideus ou os nevos azuis[8].

Apesar de poderem estar presentes à nascença, a maior parte das manifestações da doença surgem pelos 20 anos de idade, altura em que é, em média, feito o diagnóstico[5,8,6]. Dos indivíduos com diagnóstico de CNC, 70% tem um parente afectado e apenas em 30% há uma mutação genética de novo[5,6]. A maioria das mutações identificadas afectam o gene PRKAR1A, localizado no braço longo do cromossoma 17, que codifica a subunidade reguladora tipo 1α da proteína cinase A (PKA). Este gene parece actuar como gene supressor tumoral[5,6,8,11]. As mutações inactivadoras no PRKAR1A, presentes em mais de 60% destes doentes, são responsáveis pelas múltiplas neoplasias e lentiginose do CNC[12].

Métodos

Foi efectuada revisão da literatura obtida por pesquisa nas bases de dados *Pubmed* e *b-on*. Foram utilizados os termos "Carney Complex", "PRKAR1A", "cardiac myxomas", "PPNAD" e "lentiginosis". Analisaram-se 34 artigos científicos incluindo revisões gerais, de genética e casos clínicos.

Objectivos

Compilar a mais recente informação científica sobre o tema de forma a fornecer uma revisão clara e atualizada desta síndrome endócrina múltipla.

Revisão

1. Epidemiologia

O CNC é uma síndrome rara. Actualmente são conhecidos mais de 700 indivíduos com a doença[6], de todas as etnias e áreas geográficas[6,8,9,13]. Predomina no sexo feminino (≈ 60%)[7,8,9] e cerca de 70% dos casos pertencem a famílias afectadas[5,7,13]. O diagnóstico é feito entre os 20 a 30 anos, sendo a esperança média de vida de 50 anos[6,9].

2. Manifestações clínicas do CNC

Cutâneas: Estão presentes em cerca de 80% dos doentes com CNC[5,7,10]. As lesões mais frequentes correspondem a manchas pigmentadas na pele, nevos azuis epitelióides e mixomas cutâneos. Mais raramente são observadas efélides, manchas café com leite, nevos azuis atípicos, entre outras[5]. O componente cutâneo tem grande relevância para o diagnóstico porque se apresenta em idade precoce e é facilmente reconhecido,

possibilitando a detecção atempada de outras condições que possam colocar em risco a vida[7,10,13,14]. Estima-se que cerca de 80% dos doentes portadores de um mixoma cardíaco, potencialmente fatal, apresentaram um mixoma cutâneo durante a vida, sendo por isso muito importante biopsar lesões suspeitas[10].

A manifestação clínica mais comum nos doentes com CNC é a lentiginose, (manchas cutâneas pigmentadas semelhantes a efélides vulgares)[5,6,9]. Podem estar presentes ao nascimento, mas geralmente só adquirem a sua intensidade e distribuição características (lábios, zonas perioral e periocular, conjuntiva e mucosa genital) na puberdade[5,7,9]. Ao contrário das lesões cutâneas da exposição solar ou da idade, tendem a desvanecer após a quarta década de vida[10].

Os nevos azuis epitelióides, geralmente benignos[5], são também comuns no CNC, mas raros na população em geral. São pequenas lesões circulares (≈ 5 mm), de cor azul a preta, com distribuição variável na face, tronco, membros e raramente nas mãos ou pés[10].

Os mixomas cutâneos, presentes em 30-50% dos doentes, são geralmente múltiplos, predominantes nas pálpebras, canal auditivo externo e mamilos. São pequenas pápulas de aspecto opalescente ou rosa escuro, assintomáticas e diagnosticadas em média aos 18 anos, com tendência para a recorrência[6,7,10].

Cardíacas: As neoplasias primárias do coração são raras. O mixoma é o tumor cardíaco mais frequente e em cerca de 10% dos casos está associado a formas familiares[15]. É a manifestação não cutânea mais comum do CNC[7,9]. A sua dimensão pode variar de poucos milímetros a vários centímetros e podem apresentar-se parcialmente calcificados[5]. Os mixomas associados ao CNC, são muitas vezes múltiplos, em qualquer uma das câmaras cardíacas e surgem mais cedo (média aos 20 anos) do que os esporádicos[5,11]. A literatura descreve uma elevada taxa de recorrência destes tumores, com necessidade de reintervenção cirúrgica em cerca de 50% dos doentes[11,16,17,18].

O diagnóstico é feito por ecocardiografia, eventualmente ecografia transesofágica ou ressonância magnética cardíaca (RMN)[6,8].

As manifestações clínicas mais frequentes são os sintomas ou sinais resultantes da obstrução intracardíaca e os eventos embólicos cérebro-vasculares potencialmente graves. Estes eventos são a principal causa de morbilidade e mortalidade em doentes com CNC, sendo responsáveis por mais de 50% das mortes[7,9,11].

Supra-renais: A doença nodular pigmentada primária da supra-renal (PPNAD) é uma causa invulgar de síndrome de Cushing observada maioritariamente em doentes com CNC. A PPNAD foi relatada em quase todos os doentes com CNC submetidos a autópsia[11], inclusivamente em supra-renais sem sinais de hipercortisolismo, sugerindo vários graus de expressão clínica que podem ocultar a verdadeira prevalência da doença[9]. Trata-se de um tumor secretor benigno, de crescimento lento[19], presente em mais de 25% dos doentes sendo o principal tumor endócrino do CNC[20]. Nos doentes portadores da mutação no gene PRKAR1A, a síndrome de Cushing está presente em 70% das mulheres com menos de 45 anos e em 45% dos homens[6]. A distribuição etária é bimodal com diagnóstico na infância ou entre os 20-30 anos[7]. Os sinais clínicos são de hipercortisolismo. As glândulas supra-renais dos doentes com PPNAD são habitualmente de dimensão e peso normais, pelo que a tomografia computorizada (TC) só mostra alterações em um terço dos casos[9]. Macroscopicamente, são visíveis micronódulos pigmentados produtores de cortisol no córtex de ambas as supra-renais[8,9,19]. A evolução da PPNAD para malignidade é muito rara, havendo relato na literatura de apenas dois casos[20,21].

Hipofisárias: Mais de 75% dos doentes com CNC apresenta elevação dos valores de GH e do *factor de crescimento insulina like tipo 1* (IGF-I), acompanhada de ligeira hiperprolactinémia[6,9,11]. Menos de um quinto dos doentes têm tumores hipersecretores, hiperprolactinemia ou acromegalia, sendo esta última de evolução clínica lenta, mas progressiva[22], ao contrário da acromegalia causada pelos macroadenomas, detectáveis nos exames de imagem e clinicamente activa[5,9].

Em tecidos hipofisários de doentes com CNC foi observada hiperplasia, parecendo existir uma zona de transição entre o adenoma e o tecido hiperplásico que o envolve. Pensa-se que as mutações no PRKAR1A possam estar relacionadas com a hiperplasia celular, desencadeando alterações genéticas cumulativas a nível somático e originar adenomas em alguns doentes.

Tiroideias: A patologia da tiróide é comum nos doentes com CNC, sendo alta a probabilidade de detecção de alguma alteração ecográfica[22,23]. Cerca de 75% dos doentes são portadores de nódulos tiroideus, geralmente adenomas foliculares não funcionantes na primeira década de vida[6,7]. Grande parte dos doentes permanecem eutiroideus. A apresentação pode ser desde hiperplasia folicular ou alterações quísticas a formas malignas, embora o carcinoma da tiróide seja raro[5]. Se ocorrer é do tipo folicular ou papilar, desenvolvendo-se em lesões prévias, o que reforça a importância de avaliações regulares aos doentes portadores de alterações da glândula[23].

Testiculares: Tumores do estroma testicular são comuns no CNC, particularmente o tumor de células de Sertoli calcificante variante de grandes células (LCCSCT), muito raro na população em geral. No contexto da síndrome, cerca de 50% dos indivíduos do sexo masculino desenvolverá um ou mais destes tumores[24,25]. Surgem habitualmente na primeira década de vida. São geralmente multifocais, bilaterais, sem componente de tecidos moles[5,24]. O potencial maligno é muito baixo, mas não deve ser ignorado perante massas unilaterais de grandes dimensões (> 4 cm), com extensão extratesticular em doentes menos jovens (> 40 anos)[25]. Quando hormonalmente activos manifestam-se por puberdade precoce ou ginecomastia. Dificilmente são palpáveis, mas, quando o são, correspondem a massas duras e indolores. Existe um risco aumentado de infertilidade nestes indivíduos pela possível obstrução dos túbulos seminíferos, produção hormonal inadequada[5,7].

Apesar de o LCCSCT ser o tumor testicular mais frequente no CNC, tumores de células de Leydig e derivados de restos de tecido nodular adrenocortical têm sido reportados a acompanhar o LCCSCT. Os restos de tecido adrenal podem ser causa de síndrome de Cushing após adrenalectomia bilateral quando afectados por PPNAD[7,11,25].

O diagnóstico de LCCSCT, associado a outros componentes isolados do CNC, deve estimular uma avaliação clínica na procura de outros sinais do complexo.

Neuronais: Cerca de 50% dos doentes com schwanomas melanóticos psamomatosos (PMS) têm CNC, correspondendo a cerca de 10% dos doentes com o complexo. A presença dos corpos psamomatosos não é essencial e há relato de um caso de schwanoma melanótico não psamomatoso trigeminal como manifestação inaugural de CNC[6,26]. São muitas vezes multicêntricos[7]; podem surgir em qualquer parte do sistema nervoso periférico, ocorrendo preferencialmente no estômago, esófago e cadeia simpática paraespinhal. Sintomas dolorosos e de radiculopatia são frequentes. A sua detecção é feita através de TAC e RM[6,11].

Os PMS são geralmente benignos, mas estão descritas formas malignas (10%) recorrentes e metastizantes[27]. O CNC é a única condição genética, para além das neurofibromatose e schwanomatose familiar, que inclui schwanomas[6,7,11].

Mamárias: Dois tipos de tumores da mama, que podem coexistir, foram descritos em doentes com CNC: fibroadenomas mixóides, que correspondem a anormalidades do mesênquima, e adenomas ductais que são anormalidades do epitélio com tendência para a bilateralidade. Os adenomas ductais são uma entidade característica do CNC, sendo importante o diagnóstico diferencial com o carcinoma da mama. Geralmente são massas palpáveis, indolores, periareolares, assintomáticas ou associadas a escorrência mamilar. É típica a observação de calcificações na mamografia. A presença destas lesões dificulta o rastreio mamográfico do cancro da mama em doentes com CNC[5].

Ósseas: O osteocondromixoma ou tumor ósseo de Carney é um tumor benigno raro observado no contexto de CNC. Afecta preferencialmente os ossos longos ou dos seios nasais e pode ser osteolítico. É detectado durante a avaliação imagiológica de efeitos de massa que causam, por exemplo, edema, proptose, ou obstrução nasal[5,6].

Ováricas: As doentes com CNC parecem ter maior predisposição para lesões do ovário, nomeadamente quistos benignos, ecograficamente múltiplos[5,7] mas há estudos que relatam uma frequência de carcinoma do ovário superior à da população em geral[28].

Pancreáticas: Um estudo recente levanta a hipótese de uma possível associação entre CNC e tumores pancreáticos de vários tipos histológicos[29]. A maioria dos doentes identificados com tumores pancreáticos apresentava mutações inactivadoras no gene PRKAR1A. É sugerido o rastreio de patologia pancreática na avaliação dos doentes com CNC[29]. Parece haver uma maior incidência destes tumores em relação à população geral e uma apresentação em idade mais precoce (35 anos em doentes com CNC e 72 anos na população em geral).

A Tabela 1 pretende demonstrar a prevalência das diferentes componentes do CNC de acordo com a publicação de Bertherat J[8].

Genética

A proteína cinase A é um componente essencial da via de sinalização do AMPc (Figura 1) implicada no normal funcionamento de células endócrinas e outras células. Na sua forma inactiva, esta enzima é constituída por 2 homodímeros reguladores e 2 homodímeros catalíticos. Em resposta ao aumento dos níveis de AMPc, que estabelece ligação com as subunidades

Tabela 1. Prevalência das principais componentes do CNC (adaptado de Bertherat J[8].

Manifestação	%
Lentiginose	60-70%
Mixoma cardíaco	30-60%
Mixoma cutâneo	20-63%
Doença nodular pigmentada primária da supra-renal	25-60%
Tumores testiculares	33-56%
Adenoma ductal da mama	25%
Quistos do ovário	20-67%
Tumores da tiroide	10-25%
Acromegália	10%
Schwanoma melanótico psamomatoso	8-18%
Osteocondromixoma	< 10%

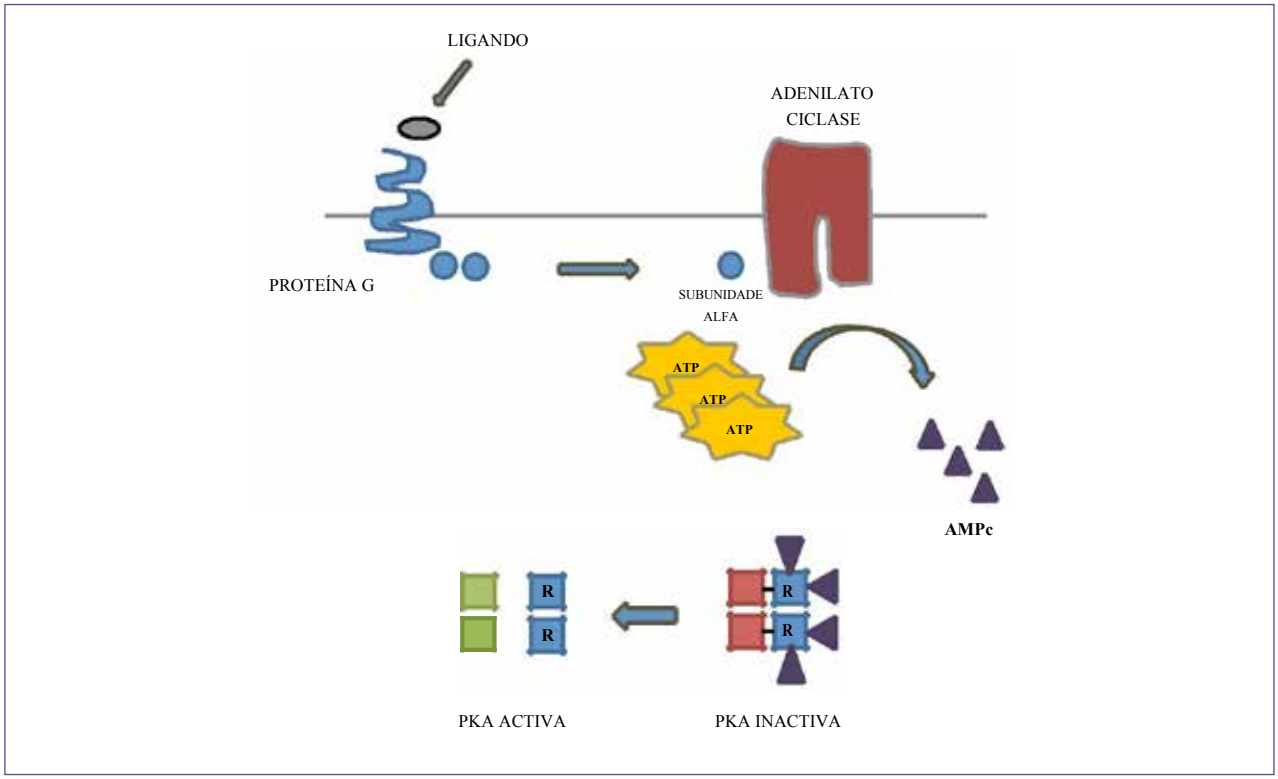


Figura 1. Via de sinalização do AMPc e o seu papel na activação da PKA, cujas subunidades catalíticas livres possuem capacidade fosforilativa. Adaptado de Grande EJL, *et al*[9].

reguladoras, há dissociação entre a componente reguladora e catalítica da molécula. As subunidades catalíticas activas são capazes de fosforilar diversas proteínas implicadas na regulação de processos celulares, como a transcrição, metabolismo, progressão do ciclo celular e apoptose[7]. Um exemplo destes mecanismos é a fosforilação intranuclear da proteína de ligação do elemento de resposta do AMPc (CREB), capaz de induzir o processo de transcrição[9]. São conhecidas 4 isoformas das subunidades reguladoras (R1A, R1B, R2A e R2B), codificadas, respectivamente, pelos genes PRKAR1A, PRKAR1B, PRKAR2A, PRKAR2B, e 3 isoformas das subunidades catalíticas (CA, CB, CG). A PKA é do tipo 1 se constituída pelas subunidades R1A e R1B, ou do tipo 2 se constituída pelas subunidades R2A e R2B[9].

Em 2000 foi estabelecida pela primeira vez a relação entre o gene PRKAR1A e o CNC[30,31] após observação de várias mutações no gene. Desde então foram identificadas 117 diferentes mutações do gene, presentes em mais de 60% dos doentes com CNC, traduzidas por substituições de bases, pequenas delecções e inserções ou rearranjos em qualquer parte do gene, sendo raras as grandes delecções[7]. As mutações na subunidade R1A são as únicas que conduziram a doença[12]. A penetrância desta síndrome nos portadores do gene PRKAR1A mutado é superior a 95% aos 50 anos de idade[6,12], sendo raro os portadores da mutação não apresentarem critérios da doença.

O CNC é geneticamente heterogéneo estando associado ao locus 17q22-q24, onde está localizado o gene PRKAR1A, e a um segundo locus 2p16 descrito por Stratakis *et al*[32], apesar do gene responsável pela doença neste locus permanecer desconhecido. Consoante o locus afectado a síndrome pode ser designada CNC tipo 1 e CNC tipo 2 respectivamente[4].

Têm sido identificadas mutações que conduzem à expressão de proteínas alteradas e que se associam a fenótipos de doença mais severa[9,33], com casos de malignidade (exemplo de um caso de tumor maligno da supra-renal numa família açoriana)[20]. Neste tipo de mutações, que correspondem a cerca de 17% de todas as mutações conhecidas, o mecanismo de degradação do mRNA mediado por mutações *nonsense* não é eficaz[12].

As alterações genéticas descritas assumem um vasto leque de fenótipos com diferentes manifestações e graus de severidade. Houve limitações nos estudos da relação genótipo-fenótipo, porque a maioria das mutações eram específicas do doente ou da família e havia grande variabilidade fenotípica[7]. Porém, foram estabelecidas algumas relações entre alterações genéticas e manifestações do CNC: doentes com mutação no gene PRKAR1A têm mais frequente e precocemente lesões cutâneas pigmentadas, mixomas, tumores tiroideus ou das gónadas, quando comparados com doentes sem a mutação. A acromegalia, mixomas cardíacos, lentiginose e PMS estão mais relacionados com mutações localizadas em exões. A mutação mais vezes descrita, c.491_492delTG, está particularmente presente em doentes com a associação de mixomas cardíacos, lentiginose e tumores da tiróide. A maioria dos casos com PPNAD isolada é portadora da mutação c.709-7del6. Por fim, nos doentes com CNC2 as manifestações da doença surgem mais tarde, não há história familiar e raramente se apresentam por mixomas,

tumores tiroideus, PMS ou LCCSCT. Apesar dos avanços no sentido de um melhor aconselhamento genético a heterogeneidade genética e clínica da doença é muito significativa[33].

O estudo genético deve ser proposto a todos os doentes com CNC e aos familiares de primeiro grau quando uma mutação no gene PRKAR1A é identificada. A presença da mutação deve orientar um seguimento semelhante ao indicado para doentes com doença clínica[8].

Diagnósticos diferenciais e diagnóstico definitivo

Os actuais critérios diagnósticos do CNC foram estabelecidos por Stratakis *et al*[11]. O diagnóstico é feito na presença de dois ou mais critérios major de doença ou, um critério major acompanhado de um critério suplementar (Tabela 2)[5-9,11]. Os critérios major devem ser alvo de confirmação histológica, bioquímica e imagiológica[7]. Alguns achados sugestivos de doença, apesar de não serem diagnósticos, implicam a realização da história do doente e da família e, eventualmente, posterior estudo clínico, laboratorial ou imagiológico[8].

Apesar dos mecanismos moleculares distintos há condições familiares cujas manifestações se podem sobrepor às do CNC. Um dos exemplos é a síndrome de McCune Albright (MAS) caracterizada por lesões cutâneas, do sistema endócrino e do esqueleto[10]. Tem em comum com o CNC anomalias da pigmentação cutânea, hiperplasia adrenocortical e hipofisária, tumores tiroideus e até mixomas; contudo, enquanto no CNC a lentiginose é a manifestação cutânea primordial, na MAS as manchas café com leite são maiores, mais pigmentadas e frequentes e não desvanecem com o tempo. No CNC a hiperplasia adrenal é micronodular e pigmentada, as lesões tiroideias são habitualmente de expressão hormonal silenciosa e os mixomas de localização cutânea, contrastando com a hiperplasia adrenal macronodular, os tumores hiper-

Tabela 2. Critérios de diagnóstico do CNC e achados sugestivos da doença (adaptado de Stratakis *et al.*[11]).

Critérios major de diagnóstico para CNC
1. Pigmentação cutânea em mancha com distribuição típica (lábios, conjuntiva, cantus interno e externo, mucosa vaginal e peniana
2. Mixoma[a] (cutâneo e mucoso)
3. Mixoma cardíaco[a]
4. Mixomatose da mama[a] ou imagens sugestivas deste diagnóstico na RM com supressão de gordura
5. PPNAD[a] ou resposta paradoxal do cortisol urinário à administração de dexametasona durante a prova de Liddle
6. Acromegália por adenoma produtor de GH[a]
7. LCCSCT[a] ou calcificações características na ecografia testicular
8. Carcinoma da tiróide[a] ou múltiplos nódulos hipoecogénicos na ecografia tiróidea em doente jovem
9. Schwanoma melanotico psamomatoso[a]
10. Nevo azul, nevo azul epitelióide[a]
11. Adenoma ductal da mama[a]
12. Osteocondromixoma[a]
[a] Após confirmação histológica
Critério suplementares
1. Familiar do primeiro grau afectado
2. Mutação inactivadora no gene PRKAR1A
Achados sugestivos de ou possivelmente associados ao CNC
1. Efélides em grande número (sem pontos pigmentados escuros ou distribuição típica)
2. Nevos azuis do tipo comum (se múltiplos)
3. Manchas café com leite ou outras marcas de nascença
4. Níveis elevados de IGF-1, prova de tolerância à glicose oral anormal, resposta paradoxal da GH à TRH na ausência de acromegália clínica
5. Miocardiopatia
6. Sinus pilonidal
7. História de síndrome de Cushing, de acromegália, ou de morte súbita na família
8. Marcas cutâneas múltiplas ou outras lesões cutâneas; lipomas
9. Pólipos no cólon (usualmente em associação com acromegália)
10. Hiperprolactinémia (geralmente moderada e quase sempre combinada com acromegália clínica ou subclínica)
11. Nódulo benigno único da tiróide em criança (<18 anos); Múltiplos nódulos tiroideus em indivíduo com mais de 18 anos
12. História familiar de carcinoma, em particular da tiróide, cólon, pâncreas, e ovário; outros tumores benignos ou malignos

secretores da tiróide e os mixomas intramusculares da MAS. A hiperplasia hipofisária é a única condição comum às duas síndromes[11,22].

O CNC tem ainda semelhanças com algumas síndromes lentiginosas, de que são exemplo a síndrome de Peutz-Jeghers (PJS), as hamartoses relacionadas com o gene PTEN (a doença de Cowden e a síndrome de Bannayan-Zonana) e a síndrome LEOPARD/Noonan. A PJS relaciona lentiginose, pólipos hamartomatosos gastrointestinais múltiplos com uma probabilidade aumentada para o desenvolvimento de neoplasias[10,34]. A distribuição e densidade das lesões de lentigo são sobreponíveis às do CNC, bem como as características apresentadas pelo LSSCST em ambas as síndromes[11].

Na síndrome LEOPARD o padrão lentiginoso pode suscitar dúvidas diagnósticas mas, ao contrário do que acontece na PJS e CNC, as lesões não ultrapassam o bordo labial. A doença de Cowden inclui, no seu espectro de manifestações, tumores foliculares da tiróide que podem integrar o CNC. Os tumores ou hiperplasia da supra-renal podem também ser observados nas síndromes de Beckwith-Wiedemann, Li Fraumeni, em casos de deficiência de 21-hidroxilase e no contexto da síndrome MEN1 que inclui ainda adenomas hipofisários[6,34].

Tratamento

A terapêutica das várias componentes do CNC deve ser ponderada em função da sintomatologia, do tamanho e localização dos tumores, das manifestações hormonais ou do grau de malignidade[8].

Os mixomas cardíacos, responsáveis por morte em 12% dos casos, necessitam de ressecção cirúrgica, para prevenir eventos embólicos potencialmente fatais. Os mixomas cutâneos e mamários são ressecáveis.

A adrenalectomia bilateral é o tratamento mais frequente e eficaz da síndrome de Cushing por PPNAD, apesar de poderem ser utilizados, em casos seleccionados, o cetoconazol ou o mitotano[8].

Os tumores hipofisários são tratados com cirurgia transesfenoidal mas, o tratamento com análogos da somatostatina pode ser útil como terapêutica inicial ou adjuvante à cirurgia.

As lesões tiroideias com suspeita de malignidade têm também indicação cirúrgica.

Para os doentes com LCCSCT e ginecomastia propõe-se orquidectomia de forma a evitar fusão epifiseal e a puberdade precoce[6-9].

Os PMS, localizados em redor das raízes nervosas ao longo da medula espinhal, são tumores frequentemente inoperáveis devido à localização. São, a par dos nódulos tiroideus, a maior causa de casos de malignidade no CNC[7,8]. As ressecções incompletas conduzem a risco de recorrência, transformação maligna e metastização[27].

Seguimento de doentes e rastreio de familiares

Os doentes com CNC ou com predisposição genética devem realizar, desde a infância, exames de rastreio anuais para as diversas manifestações da doença.

Uma ecocardiografia deve ser feita nos primeiros 6 meses de vida e depois anualmente e se o mixoma foi excisado de 6 em 6 meses[8]. Nos indivíduos pré-pubertários o ecocardiograma e o exame clínico, com um bom acompanhamento do crescimento e estado pubertário serão suficientes. Os tumores endócrinos podem ser detectados precocemente mas, em regra, só têm significado clínico durante a segunda década de vida, pelo que o estudo só deve ser solicitado se a clínica o exigir[7,11].

Em casos pós-pubertários ou adultos devem ser requisitados anualmente: um ecocardiograma, doseamento dos níveis de cortisol livre urinário (eventualmente complementados pela prova de Liddle modificada, doseamentos diurnos do cortisol plasmático ou TC da supra-renal), doseamento dos níveis de IGF-1 (com possível auxílio da PTGO, prova de estimulação com TRH ou RM) e ecografia testicular em indivíduos do sexo masculino. Numa avaliação inicial uma ecografia da tiróide, ecografia abdominopélvica, mamografia e RM da coluna deverão ser pedidas e repetidas quando necessário[6,11].

Conclusão

O CNC é uma síndrome endócrina múltipla rara com variadas manifestações, mas as alterações cutâneas são praticamente uma constante[10]. Apesar dos critérios existentes, existem dificuldades no diagnóstico diferencial com outras síndromes[34].

São achados clínicos que devem levantar a suspeita do diagnóstico a lentiginose peri-orificial ou peri-palpebral, nevus azuis múltiplos, mixomas cutâneos sobretudo se múltiplos ou diagnosticados em idade precoce e lesões cutâneas associadas a distúrbios endócrinos. A valorização de alterações cutâneas pode ser importante para um diagnóstico mais precoce, para a deteção atempada de componentes malignas e para a orientação para aconselhamento genético[13].

Na maioria dos casos, esta síndrome familiar está associada a uma mutação no gene PRKAR1A, sendo que a maior parte dos tumores observados em doentes com a mutação é benigna[19]. Contudo os doentes com CNC têm diminuição da esperança de vida essencialmente devido a complicações neoplásicas, que podem ser malignas.

Os portadores de mutações no gene PRKAR1A e de manifestações clássicas de CNC pertencem, em regra, a famílias que têm outros membros afectados[33]. O PRKAR1A tem um papel fundamental no controlo da actividade da PKA, protagonizado pelo AMPc, através de mecanismos compensatórios que asseguram a regulação equilibrada das subunidades catalíticas livres. A hiperactividade ao nível celular pode contribuir para o aparecimento de tumores endócrinos[12]. É provável que haja outros genes implicados na doença mas estão ainda mal estudadas[7].

O rastreio anual de tumores está recomendado em todos os doentes com CNC, bem como o rastreio e diagnóstico precoce de familiares geneticamente afectados ou que cumpram os critérios clínicos. Atenção especial deve ser dirigida à detecção dos mixomas cardíacos pela elevada taxa de mortalidade associada[8].

Desde 1985 foi grande a evolução do conhecimento relativo ao CNC. A inclusão das diversas patologias envolvidas numa única entidade permitiu melhorar a orientação dos doentes com CNC e dos seus familiares, contribuindo para um maior benefício clínico. Algumas correlações genótipo-fenótipo recentemente estabelecidas contribuirão para melhor definir o prognóstico da doença e o aconselhamento, abrindo novos horizontes para investigação[33].

Referências

1. Carney JA. The complex of myxomas, spotty skin pigmentation and endocrine overactivity. Medicine. 1985;64(4): 270-283.
2. Atherton DJ, Wells RS, Macdonald DM. A syndrome of various cutaneous pigmented lesions, myxoid neurofibromata and atrial myxoma: the NAME syndrome. Br J Dermatology. 1980;103:421-429.
3. Rhodes AR, Silverman RA, Harrist TJ, Perez-Athaid AR. Mucocutaneous lentigines, cardiomucocutaneous myxomas and multiple blue nevi: the LAMB syndrome. J Am Acad Dermatol. 1984;10:72-82.
4. OMIM (12/10/2010) MIM number: #160980. Johns Hopkins University, Baltimore, MD. World WideWeb URL: http://omimorg/
5. Courcoutsakis NK, Tatsi C, Patronas NJ, Lee CCR, Prassopoulos PK, Stratakis CA. The complex of myxomas, spotty skin pigmentation and endocrine overactivity (Carney Complex): imaging findings with clinical and pathological correlation. Insights into Imaging. 2013;4(1):119-133.
6. Stratakis CA, Horvath A. Carney Complex. In: Pagon RA, Bird TC, Dolan CR, Stephens K, editors. GeneReviews [Internet].Seattle (WA): University of Washington;1993-2003. [Accessed 2008 Jan 5]
7. Rothenbuhler A, Stratakis CA. Clinical and molecular genetics of Carney complex. Best Pract Res Clin Endocrinol Metab. 2010;24(3):389-399.
8. Bertherat J. Carney complex. OJRD. 2006;1:21-27.
9. Grande EJL, Martínez DK, Boillosa MG. Carney Complex. Endocrinology Nutrition. 2011;58(6):308-314.
10. Horvath A, Stratakis CA. Carney Complex and lentiginosis. Pigment Cell and Melanoma Research. 2009;22:580-587.
11. Stratakis CA, Kirschner LS, Carney JA. Clinical and molecular features of the Carney Complex: diagnostic criteria and recommendations for patient evaluation. J Clin Endocrinol Metab. 2001;86(9):4041-4046.
12. Horvath A, Bertherat J, Groussin L, et al. Mutations and polymorphisms in the gene encoding regulatory subunit type 1-alpha of protein kinase A (PRKAR1A): an update. Hum Mutat. 2010;31(4):369-379.
13. Vandersteen A, Turnbull J, Jan W, et al. Cutaneous signs are important in the diagnosis of the rare neoplasia syndrome Carney Complex. Eur J Pediatr. 2009;168(11):1401-1404.
14. Kennedy RH, Waller RR, Carney JA. Ocular pigmented spots and eyelid myxomas. Am J Ophthalmol. 1987;104(5): 533-538.
15. Teixeira R, Lourenço C, Coelho L, et al. Complexo de Carney a propósito de um caso clínico. Rev Port Cardiol. 2009;28(2):211-222.
16. Wilbring M, Wiedemann S, Kappert U, Matschke K. A complicated case of Carney complex: Fifth reoperative cardiac surgery for resection of recurrent cardiac myxoma. J Thorac Cardiovasc Surg. 2013;146:22-24.
17. Guenther F, Siepe M, Schlensak C, Aumann K, Anton A, Niesen WD. Recurrence of a familial giant multilocular cardiac myxoma in a patient with carney's complex. Circulation. 2011;123:929-932.
18. Salhab KF, Said SM, Schaff HV. Resection of multiple recurrent cardiac myxomas in an adult man with Carney's Complex. Ann Thorac Surg. 2012;93:2071.
19. Bertherat J. Adrenocortical cancer in Carney Complex: A Paradigm of Endocrine Tumor Progression or an Association of Genetic Predisposing Factors? J Clin Endocrinol Metab. 2012;97(2):387-390.
20. Anselmo J, Medeiros S, Carneiro V, et al. A Large Family with Carney Complex Caused by the S147G PRKAR1A Mutation Shows a Unique Spectrum of Disease Including Adrenocortical Cancer. J Clin Endocrinol Metab. 2012, 97(2):351-359.
21. Morin E, Mete O, Wasserman J, Joshua AM, Asa SL. Carney complex with adrenal cortical carcinoma. J Clin Endocrinol Metab. 2012;97:202-206.
22. Stergiopoulos S, Abu-Asab M, Tsokos M, Stratakis CA. Pituitary pathology in Carney Complex patients. Pituitary. 2004;7:73-82.
23. Stratakis CA, Courcoutsakis NA, Abati A, et al. Thyroid gland abnormalities in patients with the syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas (Carney complex). J Clin Endocrinol Metab. 1997;82(7):2037-2043.
24. Brown B, Ram A, Clayton P, Humphrey G. Conservative management of bilateral Sertoli cell tumors of the testicle in association with the Carney complex: a case report. Journal of Pediatric Surgery. 2007;42:13-15.
25. Washecka R, Dresner MI, Honda SA. Testicular tumors in Carney's complex. J Urol. 2002;167(3):1299-1302.
26. Carrasco CA, Rojas-Salazar D, Chiorino R, Venega JC, Wohllk N. Melanotic nonpsammomatous trigeminal schwannoma as the first manifestation of Carney complex: case report. Neurosurgery. 2006;59(6):1334-1335.

27. Shields LBE, Glassman SD, Raque GH, Shields CB. Malignant psammomatous melanotic schwannoma of the spine: a component of Carney complex. Surg Neurol Int. 2011;2:136.

28. Stratakis CA, Papagiorgiou T, Premkumar A, et al. Ovarian lesions in Carney complex: clinical genetics and possible predisposition to malignancy. J Clin Endocrinol Metab. 2000;85:4359-4366.

29. Gaujoux S, Tissier F, Ragazzon B, Rebours V, Saloustros E, Perlemoine K. Pancreatic Ductal and Acinar Cell Neoplasms in Carney Complex: A Possible New Association. J Clin Endocrinol Metab. 2011;96(11):1888-1895.

30. Kirschner LS, Carney JA, Pack SD, et al. Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney complex. Nat Genet. 2000;26(1):89-92.

31. Casey M, Vaughan CJ, He J, et al. Mutations in the protein kinase A R1α regulatory subunit cause familial cardiac myxomas and Carney complex. J Clin Invest. 2000;106:31-38.

32. Stratakis CA, Carney JA, Lin JP, et al. Carney complex, a familial multiple neoplasia and lentiginosis syndrome. Analysis of 11 kindreds and linkage to the short arm of chromosome 2. J Clin Invest. 1996;97:699-705.

33. Bertherat J, Horvath A, Groussin L, et al. Mutations in regulatory subunit type 1A of cyclic AMPdependent protein kinase (PRKAR1A): phenotype analysis in 353 patients and 80 different genotypes. J Clin Endocrinol Metab. 2009;94:2085-2091.

34. Lodish MB, Stratakis CA. The differential diagnosis of familial lentiginosis syndromes. Fam Cancer. 2011;10(3): 481-490.

Artigo de revisão

Morbilidade relacionada com terapêutica oncológica em sobreviventes de cancro a longo prazo – uma revisão

Cancer-therapy-related morbidity in long-term cancer survivors: a review

Autores
Fernando Gonçalves[1], Sara Raquel Martins[2], João Neves[2], Manuel Magalhães[1], Estrela Rocha[1], António Araújo[1]

Afiliação:
[1]Serviço de Oncologia Médica, [2]Serviço de Medicina Interna, Centro Hospitalar e Universitário do Porto, Portugal

Conflitos de interesse:
No conflicts of interest to report

Autor para correspondência:
Fernando Gonçalves –
Serviço de Oncologia Médica,
Centro Hospitalar e Universitário do Porto,
Largo do Prof. Abel Salazar 4099-001.
Email: fernando_goncalves@hotmail.com

Resumo:

Os avanços no diagnóstico e tratamento estão a tornar o cancro numa doença crónica manejável. Juntamente com o aumento da sobrevida, surgem, actualmente, as complicações de longo termo. Estas parecem ser comuns e podem ser potencialmente fatais ou afectar profundamente a qualidade de vida. Apresentamos dois casos clínicos com três diagnósticos de cancro, relacionados com terapêuticas oncológicas prévias e revemos os mecanismos subjacentes. Ainda que as neoplasias secundárias tenham já sido descritas como consequência de terapêuticas oncológicas, não existem exames de rastreio estabelecidos especificamente para os sobreviventes de cancro de longa data. Além disso, muitos efeitos secundários crónicos multisistémicos podem surgir durante a vigilância destes indivíduos. Métodos de rastreio de neoplasias secundarias, baseados na evidência são necessários para uma mais adequada vigilância.

Palavras-chave: Sobreviventes de cancro, Qualidade de vida, Segunda neoplasia, Neoplasia secundária

Abstract:

Advances in diagnosis and treatment are turning cancer into a manageable chronic disease. However, alongside the improved survival, long-term complications are emerging. They seem to be common and can possibly be life-threatening or deeply affect quality of life. We present two clinical cases with three cancer diagnoses where cancer is related to previous oncologic therapies, and review the mechanisms of this association. Although secondary cancers have been described as a consequence of cancer therapy, there are no screening protocols specifically designed for long-term cancer survivors (LTCS). Many other multisystemic chronic side effects may emerge during the follow-up of LTCS, which healthcare professionals are increasingly required to identify and treat. Evidence-based guidance on screening secondary cancers and non-oncologic morbidity are needed for better long-term follow-up of these patients.

Keywords: *Long-term cancer survivors, Second cancer, Secondary malignancy, Survivorship, Quality of life*

Introduction

With the ongoing advances in oncology research and treatment, overall survival is increasing and cancer is turning into a chronic manageable disease. Therefore, the number of long-term cancer survivors (LTCS), and the incidence of second primary malignancies, are increasing.[1,2] Despite the well-known cancer treatment toxicities, cancer itself is one of the rarest and, thus, least described ones, either from chemotherapy (CT) agents, radiotherapy (RT) or endocrine therapy (ET). LTCS may be at an increased risk for developing (1) a second malignancy due to previous treatments; and (2) other non-oncologic complications. We present two clinical cases with three cancer diagnoses where the cancer is related to previous oncologic therapies, and discuss the aspects related to the cancer treatment as a known aetiology. Non-oncologic morbidity related to cancer therapy will also be addressed.

Methods

The authors reviewed the theme of cancer therapy-related morbidity. A PubMed search was made focusing on the terms 'second cancer', 'long-term cancer survivors', 'secondary malignancy' and 'survivorship'. A revision of the bibliography of the main articles was performed. Two clinical cases of proven cancer-therapy-related second neoplasms were selected from in-hospital databases and are described to illustrate the subject.

Clinical Case 1

A 39-year-old woman, a long-time smoker with an otherwise unremarkable medical history, presented with retrosternal pain and was diagnosed with intrathoracic non-Hodgkin disease. She was treated with a combination of CT and RT, protocol, doses and schedule unbeknownst in her clinical data.

Twenty years later, at the age of 59, she presented with haemoptysis; a chest computed tomography showed a pulmonary mass in the right upper lobe. A lung biopsy revealed a multifocal bronchioloalveolar mucinous carcinoma, CK7+, CK20-, TTF-1-, Stage IIIa. She underwent right pneumonectomy and adjuvant CT with cisplatin and vinorelbine for four cycles. Besides an infectious complication on the postpneumonectomy space, which was treated with antibiotics and chest drainage, she remained clinically stable and disease free.

Four years later at the age of 63, she had a left cervical cyst removed, which was revealed to be a cystic lymphangioma. One year later, during the imagiological follow-up, a right parotid node was detected. A biopsy revealed a mucoepidermoid carcinoma, and a suprafacial right parotidectomy was performed. No adjuvant treatment was applied and the patient maintains clinical surveillance.

At the time of writing (25, 4 and 2 years from the time of diagnosis of the first, second and third primary tumours, respectively), the patient was 65 years old, had a cardiomyopathy of unknown aetiology (presumably related to CT cardiotoxicity) with a reduced ejection fraction and a depressive disorder (secondary to the oncologic diagnosis). Regular surveillance is being maintained, and there is no clinical or imagiological evidence of any of the three malignancies. Even with optimal medical therapy, the patient still has minor symptoms of heart failure (New York Heart Association Class I), despite a reduced ejection fraction.

Clinical Case 2

A previously healthy 20-year-old woman presented with cervical node enlargement. An excisional cervical lymph node biopsy was performed, confirming the diagnosis of Hodgkin disease (nodular sclerosing variant, stage IIA). She underwent CT with Adriamycin, bleomycin, vinblastine and dacarbazine (ABVD protocol), followed by mantle field RT. When she was 23 the disease relapsed on the left supraclavicular lymph node chain; she underwent CT with chlorambucil, etoposide, procarbazine and prednisone (LEPP protocol), and the affected area was re-irradiated. Regular surveillance was maintained for 16 years, and the patient remained disease free and was discharged from further follow-up at 39 years old.

At the age of 43, she was readmitted to the oncology department due to a left breast node and right sternoclavicular joint swelling. Biopsies were performed at both sites and a double synchronous cancer diagnosis was made: (1) a left breast ductal invasive carcinoma 'Luminal A-like', Stage IIB, which was treated with a simple left mastectomy plus axillary clearance; and (2) a right clavicular pleomorphic high-grade sarcoma, which was surgically resected. She underwent adjuvant CT with cisplatin and ifosfamide, with disease progression (de novo pleural and mediastinal metastases) at 45 years old. Subsequently, second-line CT ensued (gemcitabine and docetaxel), with pulmonary and pleural disease progression during the same year, conditioning relapsing malignant pleural effusion. Due to disease progression with respiratory failure and physical frailty, the best supportive care was implemented and she succumbed to the disease later that same year.

Discussion

Currently, oncology applies what is called 'personalised medicine'. In the past, most patients with a specific type and stage of cancer received the same treatment. Now, beyond histology, the decision is based upon comorbidities, age, performance status, cancer stage, molecular and genetic profiles, and many other distinctive factors, enabling a broad range of single or combined therapeutic modalities for each specific malignancy. The multitude of possible therapies requires a substantial awareness of the eventual complications. Generally, physicians are well trained to deal with acute complications of cancer treatments. With a rise in the life expectancy of cancer survivors, healthcare professionals are increasingly required to treat chronic complications too.

Cancer is a possible side effect of cancer treatment and this is valid for either RT, CT or even ET, such as tamoxifen.[3] Only immunotherapy has not yet been correlated with the appearance of cancer.

T utilises ionising radiation (x-rays) to damage cancer cells by disrupting cell membranes, cytoplasm or the nucleus, altering normal molecular and cellular functions, which ultimately can lead to cell death. For a long time RT has been reported as an inductor of second malignancies.[4,5] Most information about radiation-induced cancers has come from the long-term Life Span Study,[6] which was set up in 1950 and is still ongoing, tracking cancer incidence and mortality in a cohort of more than 85,000 Japanese atomic bomb survivors who were exposed in 1945, at the Hiroshima and Nagasaki bombings.[7] Cancer survivors, nuclear workers, uranium miners, and people exposed during radiation accidents – such as that at Chernobyl – have been, and are being, followed-up to provide better assessments of the risk.

Currently, this matter is of increasing concern since for most cancer types treated with RT, at least 75% are treated with intent to cure the cancer, rather than to control the growth or relieve the symptoms.[8] Also, nearly two-thirds of all cancer patients will receive RT during their illness,[9] highlighting the widespread use of this technique and the necessary awareness of the possible adverse effects.

Ionising radiation is both an initiator and promoter of carcinogenesis, most probably because of the induction of genetic instability in cells, through various means: (1) the mutations of genes involved in the control of DNA synthesis or DNA repair; (2) the induction of chromosome instability; (3) the persisting aberrant production of oxygen radicals that can damage DNA; (4) the prolonged inflammatory processes in tissues; and (5) the epigenetic effects.[10] The risk is higher for people exposed at a younger age and increases with attained age. Initially, risk increases with the dose received, but seems to decline at higher doses.[11]

Classic CT drugs act against cancer cells and cause toxic damage through their effects on DNA. They also can cause mutations and chromosomal damage, contributing to the initiation, promotion and progression stages of the carcinogenic process – similarly to RT. These properties are shared with known carcinogens, such as carbamic acid or nitrosamines present in tobacco smoke.

Carcinogenesis requires time to happen, and evidence has shown that there is a latent period between the exposure to a chemical and the appearance of cancer.[12] The most common time of presentation of second malignancies related to anti-cancer drugs is 2 to 6 years after the initiation of chemotherapy, but individual and specific characteristics, such as inherent immune response or different cumulative toxic doses, can shorten or extend this interval; thus, cancer may manifest decades after the initial treatment.[13]

Alkylating agents (e.g. cyclophosphamide, ifosfamide or melphalan) are the most commonly implicated as the cause of second malignancy, and there is increased risk if patients also receive radiation.[13]

In the past, the platinum compounds (e.g. carboplatin or cisplatin) have generally not been considered human carcinogens, but patients treated with platinum-based regimens for ovarian and testicular cancer showed significantly increased risks of leukaemia in multivariable analyses that took into account other treatment factors.[14,15]

Many of the second malignancies are hematologic, but solid tumours have been reported (e.g. breast or lung cancers) as some of the most common malignancies after both Hodgkin and non-Hodgkin disease.[16,17] In fact, several studies have shown lung cancer as the most common second malignancy among non-Hodgkin disease patients, with risks raised by 36% to 90%.[18,19]

Specifically, non-Hodgkin disease, such as in Case 1, is treated with a combination of high-dose alkylating agents, platinum compounds, other chemotherapies, and RT, highlighting the risk of second malignancies in the population affected by this clinical entity.

Such facts draw attention to the lack of screening protocols designed specifically for LTCS. They are more likely than people without cancer to receive screening test associated with their cancer within 5 years of diagnosis, but this represents screening for recurrence, not a concern specifically addressed to secondary cancers.[20] Because of their augmented risk for secondary malignancies, there is an urge to improve the long-term follow-up of cancer survivors – including cancer screening – to optimise health outcomes. Evidence shows that low-dose computed tomography scanning for patients at high risk for lung cancer allows the discovery of disease with a higher percentage at the early stage.[21] This has resulted in guidelines for screening within high-risk groups.[22]

Alongside secondary cancers, multisystemic, chronic dysfunctions that might be life-threatening or deeply affect quality of life (QoL) are a worrisome problem that should come to the attention of clinicians as a long-term consequence of cancer treatment.

Central and peripheral nervous system side effects are some of the most well-known toxicities and dramatically affect patients' QoL. Emerging evidence indicates that cancer *per se* and/or cancer treatments in addition to CT may contribute to cognitive impairment – an effect also known as 'chemo-brain' or 'chemo-fog.'[23] Persistent cognitive changes associated with CT and/or hormonal therapy are often subtle, but can impact on survivors' ability to function.[24] Several meta-analyses[25-27] have concluded that there is evidence for cognitive changes associated with cancer and cancer treatments. The aetiology of cognitive impairment after CT remains unknown, although a number of mechanisms have been postulated,[28] including direct neurotoxic effects (e.g. injury to neurons or surrounding cells, altered neurotransmitter levels); oxidative stress and DNA damage; induced hormonal changes; immune dysregulation and/or release of cytokines; and blood clotting in small central nervous system vessels. Also, there seems to be a genetic predisposition in some patients.

Adult survivors of childhood cancers who received cranial RT may have reduced cognitive status, with reduced integrity in neuroanatomical regions essential in memory formation, which is consistent with early onset mild cognitive impairment.[29] Affected cognitive domains include learning, memory, processing speed, attention and executive function.[30]

Cardiovascular toxicity is one of the most common adverse events and includes coronary artery disease, valvular disease, cardiomyopathy, chronic pericardial disease and conduction abnormalities.[31] All of these can be secondary to radiation, with a particularly high incidence of cardiac disease and mortality among women who received RT for breast cancer during the second half of the 20th century, especially following RT for left-sided breast cancer. Contemporary treatments tend to rely on smaller radiation doses, and customised tangential field borders or advanced RT techniques (e.g. intensity modulated RT) are used to minimise the radiation dose delivered to the heart. Even so, some high-dose radiation seems inevitable and the effectiveness on minimising cardiac disease is yet to be proven in the years to come. Most studies pointed out that the risk of cardiac disease increased with follow-up – even after 25 years – emphasizing the importance of long-term surveillance.[32]

CT can also induce serious damage to the heart. Anthracyclines comprise a well-known and widely used anticancer drug class and their cardiotoxicity persists as a major cause of morbidity and mortality in survivors; this remains the major limitation to their application.[33]

Chronic cardiotoxicity can be classified as early (within 1 year of the termination of treatment) or late (after 1 year of treatment discontinuation), and may arise even 20 years after the exposure, once more pointing out the relevance of long-term follow-up. The most typical chronic cardiotoxicity findings are asymptomatic systolic or diastolic cardiac dysfunction, which may progress to overt heart failure.[31,33] The risk of cardiovascular disease is enhanced in a cumulative dose-dependent form, and currently there is an effort to use the lowest possible doses and the least toxic agents.[34,35] Other cardioprotective strategies (e.g. administration of dexrazoxane, angiotensin antagonists, statins or b-blockers) given on a prophylactic basis to patients on chemotherapy seem to have a modest effect (an average 32% relative risk).[33]

Although anthracyclines remain the most cardiotoxic chemotherapeutic agents, other drugs can cause cardiovascular disease (e.g. cyclophosphamide or trastuzumab) – the latter showing reversibility on the cardiac damage.[33]

The lung is also a frequently affected organ, with RT-induced lung injury being observed in 5% to 20% of patients with lung cancer. Pulmonary irradiation can cause acute and delayed side effects, which can be severe enough to lessen the survival benefit of RT. Pulmonary fibrosis may occur approximately 6 months after ending the treatment and generally stabilises in 2 years, rarely leading to chronic restrictive respiratory failure.[36] Many factors may influence the severity of lung damage, including the volume of irradiated tissue, the radiation dose, the number of fractions into which the radiation dose was divided, the adjuvant use of CT and the pre-existing lung disease or genetic predispositions.[37]

Renal function can also be impaired in the setting of cancer treatment. Chronic kidney disease is an important long-term complication of haematopoietic cell transplantation (HCT), occurring in 15% to 20% of patients who received an allogeneic HCT.[38] This is thought to be related to a low-grade renal thrombotic microangiopathy.[39]

Thyroid altered function may be seen after radiation, immunotherapy, treatment with tyrosine kinase inhibitors (e.g. imatinib, sunitinib or pazopanib)[40] or, rarely, after CT. Also, an association between hypothyroidism has been documented with fewer systemic adverse effects.[41] The authors suggest that this effect might be related to an adaptive response, protecting the body against the tissue damage of therapies by down-regulating cellular metabolism; however, more studies are needed to prove such a relationship. In a similar way, several articles relate the influence of thyroid function with the efficacy of cancer therapy, with a longer survival reported in patients who experienced hypothyroidism as a side effect; however, such results still need validation in larger cohorts.[41,42]

Osteoporosis can follow a variety of cancer therapies (hormonal therapy, CT and glucocorticoids) and early implementation of bisphosphonates and lifestyle modification should be weighed up in high-risk patients.[43]

Although this is often overlooked, the psychiatric/psychologic side effects of cancer treatment are of absolute importance in a patient's QoL. Besides the fear of disease progression or recurrence, cancer therapy itself can result in major self-perception changes (e.g. mastectomy, loss of a limb or even hair loss), loss of autonomy (by systemic side effects, neurologic impairment), loss of communication capability (e.g. deafness) or even loss of life pleasures (e.g. the capability of eating or sexual dysfunction). Therefore, the high incidence of anxiety and depression among oncology patients does not come as a surprise, and much effort has been directed to identify and treat these impairing symptoms.[44]

Sexuality and fertility also can be affected by cancer treatment. Sexual dysfunction is a frequent long-term side effect. Men frequently have erectile dysfunction related to damage to the autonomic nervous system and/or reduced circulation of blood to the penis, or hormonal impairment of sexual function. Female sexual dysfunction is frequently associated with sudden premature ovarian failure or direct effects of RT fibrosis or scar tissue causing pain with sexual activity.[45] The lack of validated interventions for sexual rehabilitation after cancer is a problem that should be addressed more consistently by oncology societies.

Conclusions

It has long been known that cancer treatments, such as CT and RT, can cause many chronic side effects, including secondary cancers. Even so, there are no screening protocols specifically designed for secondary cancers in LTCS. This should be of crucial concern since the cancer survivor population is increasing, and most of these therapies are widely used for the majority of malignancies.

The time has come to encompass long-term complications — both secondary cancer and non-oncologic morbidity — in these decisions.

We urge stakeholders to incentive research on this subject in LTCS cohorts in order that evidence-based guidance on screening secondary cancers and non-oncologic morbidity may be provided.

Disclosures

No funding or sponsorship was received for this study or publication of this article.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval to the version to be published.

This article does not contain any new studies with human or animal subjects performed by any of the authors.

Patients and/or legal representatives consented to the publication of their clinical cases for scientific purposes.

All named authors declare that they have no conflict of interest.

References

1. de Moor JS, Mariotto AB, Parry C, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. Canc Epidemiol Biomarkers Prev. 2013;22(4):561-570.
2. Hewitt M, Greenfield S, Stovall E. From cancer patient to cancer survivor - lost in transition.Committee on Cancer Survivorship: Improving Care and Quality of Life National Cancer Policy Board, 2006.
3. Curtis RE, Boice JD Jr, Shriner DA, Hankey BF, Fraumeni JF Jr. Second cancers after adjuvant tamoxifen therapy for breast cancer. J Nat Canc Inst. 1996;88:832-834.
4. Kumar S. Second malignant neoplasms following radiotherapy. Int J Environ Res Publ Health. 2012; 9(12):4744-4759.
5. Zablotska LB, Matasar MJ, Neugut AI. Second malignancies after radiation treatment and chemotherapy for primary cancers. Cancer Survivorship. New York, NY: Springer, 2007; pp 225-237.
6. Socol Y, Dobrzyński L. Atomic bomb survivors life-span study: insufficient statistical power to select radiation carcinogenesis model. Dose Response. 2015;13(1).
7. Ozasa K, Shimizu Y, Suyama A, et al. Studies of the mortality of atomic bomb survivors, report 14, 1950–2003: an overview of cancer and noncancer diseases. Radiat Res. 2012;177(3):229–243.
8. Smart DR. Physician characteristics and distribution in the U.S. 2008 Edition.
9. Facts and Figures. 2014. www.astro.org
10. Aypar U, Morgan WF, Baulch J. Radiation-induced epigenetic alterations after low and high LET irradiations. Mutat Res Fund Mol Mech Mutagen. 2011;707(1–2):24-33.
11. Gilbert ES. Ionizing radiation and cancer risks: what have we learned from epidemiology? Int J Radiat Biol. 2009;85(6):467-482.
12. Richardson DB, Cole SR, Chu H, Langholz B. Lagging exposure information in cumulative exposure-response analyses. Am J Epidemiol. 2011;174:1416-1422.
13. Tannock I, Hill R, Bristow R, Harrington L. The Basic Science of Oncology (Fifth Edition). McGraw Hill Education; 2013
14. Travis LB, Holowaty E, Hall P, Lynch CF. Risk of leukemia following platinum-based chemotherapy for ovarian cancer. New Engl J Med. 1999;340(5):351-357.
15. Travis LB, Andersson M, Gospodarowicz M, et al. Treatment-associated leukemia following testicular cancer. J Nat Canc Inst. 2000;92(14):1165-1171.
16. Ng AK, Bernardo MVP, Weller E, et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. Blood. 2002;100:1989-1996.
17. Travis LB, Curtis RE, Boice Jr JD, Benjamin F. Hankey and Joseph F. Fraumeni Jr. Second cancers following non-Hodgkin's lymphoma. Cancer. 2002;67:1991-2009.
18. Greene MH, Wilson J. Second cancer following lymphatic and hematopoietic cancers in Connecticut, 1935-82. Natl Cancer Inst Monogr. 1985;68:191-217.
19. Travis LB, Curtis RE, Glimelius B, et al. Second cancers among long-term survivors of non-Hodgkin's lymphoma. J Natl Cancer Inst. 1993;85:1932-1937.
20. Schumacher JR, Witt WP, Palta M, et al. Cancer screening of long-term cancer survivors. J Am Board Fam Med. 2012; 25(4):460-469.
21. The International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med. 2006;355:1763-1771.
22. Wiener RS, Gould MK, Arenberg DA, et al. An official American Thoracic Society/American College of Chest Physicians policy statement: implementation of low-dose computed tomography lung cancer screening programs in clinical practice. Am J Respir Crit Care Med. 2015;192:881-891.
23. Aluise CD, Sultana R, Tangpong J, et al. Chemo brain (chemo fog) as a potential side effect of doxorubicin administration: role of cytokine-induced, oxidative/nitrosative stress in cognitive dysfunction. Adv Exp Med Biol. 2010;678:147-156.
24. Vardy J, Wefel JS, Ahles T, Tannock IF, Schagen SB.Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop. Ann Oncol. 2008;19(4):623-629.

25. Anderson-Hanley C, Sherman ML, Riggs R, et al. Neuropsychological effects of treatments for adults with cancer: a meta-analysis and review of the literature. J Int Neuropsychol Soc. 2003;9:967-982.

26. Jansen CE, Miaskowski C, Dodd M, et al. A meta-analysis of studies of the effects of cancer chemotherapy on various domains of cognitive function. Cancer. 2005;104:2222-2233.

27. Stewart A, Bielajew C, Collins B, et al. A meta-analysis of the neuropsychological effects of adjuvant chemotherapy treatment in women treated for breast cancer. Clin Neuropsychol. 2006;20:76-89.

28. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Canc. 2007;7(3):192-201.

29. Armstrong GT, Reddick WE, Petersen RC, et al. Evaluation of memory impairment in aging adult survivors of childhood acute lymphoblastic leukemia treated with cranial radiotherapy. J Nat Canc Inst. 2013;105(12):899-907.

30. McDuff SG. Neurocognitive assessment following whole brain radiation therapy and radiosurgery for patients with cerebral metastases. J Neurol Neurosurg Psychiatr. 2013;84:1384-1391.

31. Curigliano G, Cardinale D, Dent S, et al. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. CA: Canc J Clin. 2016;66:309-325.

32. Bouillon K, Haddy N, Delaloge S, et al. Long-term cardiovascular mortality after radiotherapy for breast cancer. J Am Coll Cardiol. 2010;57(4):445-452.

33. Lipshultz SE, Karnik R, Sambatakos P, et al. Anthracycline related cardiotoxicity in childhood cancer survivors. Curr Opin Cardiol. 2014;29(1):103-112.

34. Dolci A, Dominici R, Cardinale D, et al. Biochemical markers for prediction of chemotherapy-induced cardiotoxicity: systematic review of the literature andrecommendations for use. Am J Clin Pathol. 2008;130:688-695.

35. Kalam K, Maradiotherapyrwick TH. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. Eur J Canc. 2013;49(13):2900-2909.

36. Chargary C, Riet F, Mazevet M, et al. Complications of thoracic radiotherapy. La Presse Médicale, 2013;42:342-351.

37. Ding N, Li J, Sun L. Molecular mechanisms and treatment of radiation- induced lung fibrosis. Current Drug Targets. 2013;14:1347-1356.

38. Zager RA. Acute renal failure in the setting of bone marrow transplantation. Kidney Int. 1994;46:1443-1458.

39. Cohen EP. Renal failure after bone-marrow transplantation. Lancet. 2001;357:6-7.

40. Eke K, Turkmen Y, Temizel M, et al. Serum resistin and insulin-like growth factor-1 levels in patients with hypothyroidism and hyperthyroidism. J Thyroid Res. 2013;2013:306-750.

41. Groot S, Janssen L, Charehbili A, et al. Thyroid function alters during neoadjuvant chemotherapy in breast cancer patients: results from the NEOZOTAC trial (BOOG 2010-01). Breast Canc Res Treat. 2015:149:461-466.

42. Sabatier R, Eymard JC, Walz J, et al. Could thyroid dysfunction influence outcome in sunitinib-treated metastatic renal cell carcinoma? Ann Oncol. 2012;23:714-721.

43. Guise TA. Bone loss and fracture risk associated with cancer therapy. Oncologist. 2006;11(10):1121-1131.

44. Mehta R, Roth A. Psychiatric considerations in the oncology setting. CA: Canc J Clin. 2015;65(4):300-314.

45. Schover LR. Sexuality and fertility after cancer. Hematology Am Soc Hematol Educ Program. 2005; 2005(1):523-527.

Artigo de investigação original

Cancro da mama: valor dos testes de estadiamento 5 anos após o diagnóstico

Breast cancer: value of staging tests 5 years after diagnosis

Autor:
Alina Rosinha, Cláudia Vieira, Maria Cassiano, Marta Ferreira, Filipa Ferreira Pereira, Susana Sousa, Deolinda Pereira

Afiliação:
Medical Oncology Department, Francisco Gentil Portuguese Institute of Oncology, Porto, Portugal

Conflitos de interesse:
None

Autor para correspondência:
Cláudia Vieira,
Medical Oncology Department, Instituto Português de Oncologia do Porto Francisco Gentil (IPO-PORTO), Rua Dr. António Bernardino de Almeida, 4200-072 Porto – Portugal. Tel: 351 22 508 40 00 (ext. 7627);
Fax: 351 22 508 40 01;
Email: claudiampvieira@gmail.com.
https://orcid.org/0000-0001-5396-9753

Resumo

Objectivos: O impacto do estadiamento na história natural e na sobrevida do cancro de mama, em pacientes assintomáticos após 5 anos de seguimento permanece desconhecido. Nos estadios II e III, a prevalência de doença metastática num tipo de exame complementar de diagnóstico superior a 1% foi considerada significativa e indica um benefício na inclusão desse exame no estudo de estadiamento. Os autores pretendem analisar o valor diagnóstico de testes de estadiamento em pacientes assintomáticos, 5 anos após o diagnóstico de cancro de mama.

Métodos: Análise retrospectiva de pacientes diagnosticados com cancro de mama em 2005, após 5 anos de seguimento e / ou hormonoterapia adjuvante e submetidos a estadiamento na nessa data.

Resultados: Incluídos 228 pacientes, 222 do sexo feminino, com idade mediana de 57 anos. Os tipos histológicos mais frequentes foram carcinoma ductal invasor (80,7%); 90,5% apresentavam recetores hormonais positivos. Os estadios mais representados foram o estadio I (29,8%) e o II (48,2%). O estadiamento após 5 anos de seguimento identificou metástases em 8 pacientes (3,5%): 5 em estadio III e 3 em estadio II. O único exame de estadiamento que teve uma taxa de detecção significativa (2%) foi a cintigrafia óssea. O marcador tumoral deve ser interpretado com cautela, pois, embora essa taxa seja significativa (2,3%), a taxa de falsos positivos é elevada (15%).

Conclusões: Estes achados achados indicam que os exames de estadiamento para detectar metástases em pacientes assintomáticas cinco anos após o diagnóstico e tratamento do cancro de mama não serão necessários em pacientes em estadio I. Nos estágios II e III, a prevalência de metástases nestes exames foi superior a 1%, pelo que a taxa de detecção foi considerada significativa, o que indica um benefício em fazê-lo rotineiramente. Para consolidar estas conclusões deverá ser estudada uma amostra maior nos estádios II e III.

Palavras-chave: Mama, Cancro, Estadiamento, Recidiva, Seguimento

Abstract

Background: *The impact of staging on breast cancer natural history and survival in asymptomatic patients after 5 years of surveillance is unknown.*

Objective: *Analyse the diagnostic value of re-staging tests in asymptomatic patients 5 years after the diagnosis and treatment of breast cancer.*

Methods: *Retrospective analysis was undertaken of patients diagnosed with breast cancer in 2005 after a 5-year follow-up and/or adjuvant hormone therapy and who underwent staging at that time.*

Outcomes: *222 patients were female and 6 were male patients weress included a median age of 57 years. The most frequent histological type was invasive ductal carcinoma (80.7%), 90.5% were hormonal-receptor positive. The most represented stages were I (29.8%) and II (48.2%). Staging after 5 years of follow-up identified metastasis in eight patients (3.5%): five in stage III and three in stage II. The only restaging exam that had a significant detection rate (2%) was bone scanning. The detection rate was 2.3% however it has to be interpreted with caution because the rate of false positives is elevated (15%).*

Conclusions: *These findings indicate that a complete restaging work-up to detect metastases in asymptomatic patients 5 years after the diagnosis and treatment of breast cancer seems unnecessary in patients in stage I. In stages II and III, the prevalence of metastatic disease with these exams was more than 1%, which—according to the detection rate is considered as significant—indicates a benefit in doing it routinely. To consolidate these findings/conclusions, a large sample in stage II and III should be evaluated.*

Keywords: *Breast, Cancer, Staging, Recurrence, 5-year follow-up*

Introduction

Breast cancer is the most frequent malignancy in women. The European prevalence estimated in 2012 was 1,814,572 cases. Due to the increasing in breast cancer, the prevalence is increasing too. In the majority of occidental countries, mortality is decreasing, especially in younger patients, due to better management of the disease and early detection. Nevertheless, breast cancer is still the most prevalent cause of death from cancer among European women.[1, 2]

In 2010, 6541 women were diagnosed with breast cancer in Portugal (incidence 118.5/100,000 habitants). It represents one-third (31.1%) of tumours diagnosed in Portuguese women.[3]

The diagnostic workup for early breast cancer is still under discussion. The probability of detection of metastasis particularly in stage I and II is low and may not justify the adverse events of computed tomography (CT) or bone scanning (BS).

Worldwide, BS, liver ultrasonography (LUS) and chest x-ray (CXR) are still commonly used in patients with newly diagnosed breast cancer as part of the baseline staging.[4-6]

The European Society for Medical Oncology (ESMO) guidelines states that the assessment of metastatic disease should be done by physical examination. Other tests are not routinely recommended, unless the disease is locally advanced or when there are symptoms suggesting metastases.[5,7,8] Blood workup (a full blood count, liver and renal function tests, plus alkaline phosphatase and calcium levels) is recommended before surgery and systemic (neo) adjuvant therapy. A CT scan of the chest, an abdominal ultrasound or CT scan and a BS can be considered for patients with: clinically positive axillary nodes, large tumours (e.g. ≥5 cm), aggressive biology (e.g. negative hormone receptors or HER positive), clinical signs, symptoms or laboratory abnormalities suggesting the presence of metastases.[5,8-10]

According to American guidelines, high-risk patients require a CXR, LUS or liver CT and BS prior to the initiation of treatment to rule out the presence of metastases.[6, 9-13]

In asymptomatic patients after 5 years of follow-up or after completing hormone therapy, there is no evidence-based literature regarding the usefulness of doing re-staging exams.[14-17]

In our institution, it has been clinical practice in the past to do some diagnostic tests (BS, LUS, CXR) before discharging and referring these patients to surveillance in the primary health care system.

The purpose of this work was to analyse the diagnostic value of these re-staging exams in asymptomatic patients 5 years after the diagnosis and treatment of invasive breast cancer.

Materials and methods

We conducted a retrospective study of a series of patients who were referred to our institution with the diagnosis of invasive breast cancer during 2005, and who had completed 5 years of follow-up or endocrine treatment and had been submitted to restaging exams before being referred to continue surveillance in the primary health care system. Extrapolating from the initial staging studies, we considered detection rates to be significant when superior to 1%.

We analysed the prevalence of the diagnosis of metastatic disease after these exams in each stage.[18] For each diagnostic test (BS, LUS, CXR), we analysed the prevalence of positive results. This was defined as the number of patients with a diagnosis of metastatic disease after an imaging technique divided by the total number of patients tested. In addition, sensitivity and specificity were calculated. The initial suspicion of secondary lesions was confirmed by other tests (bone x-ray, CT scan or magnetic resonance imaging) in order to identify 'true' positive diagnoses. Ethical considerations respected the local and national ethics committees and the Helsinki Declaration, and local ethical approval was obtained.

Statistical analysis

Data were analysed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL). For categorical variables analysis the Chi-square test was applied and for significant variables, the log-rank test was used. Differences between groups with $p < 0.05$ were considered statistically significant.

Results

Of the 751 patients admitted in 2005, 228 had been submitted to BS, LUS and CXR 5 years after being diagnosed and treated for their breast cancer (222 patients were female and 6 were male). The median age was 57 years (23–90 years). The more frequent histological type was invasive ductal carcinoma (80.7%); most of the patients had positive hormone receptors (90.5%); the HER-2 status was unknown in the majority of the patients, since its determination only started to be performed

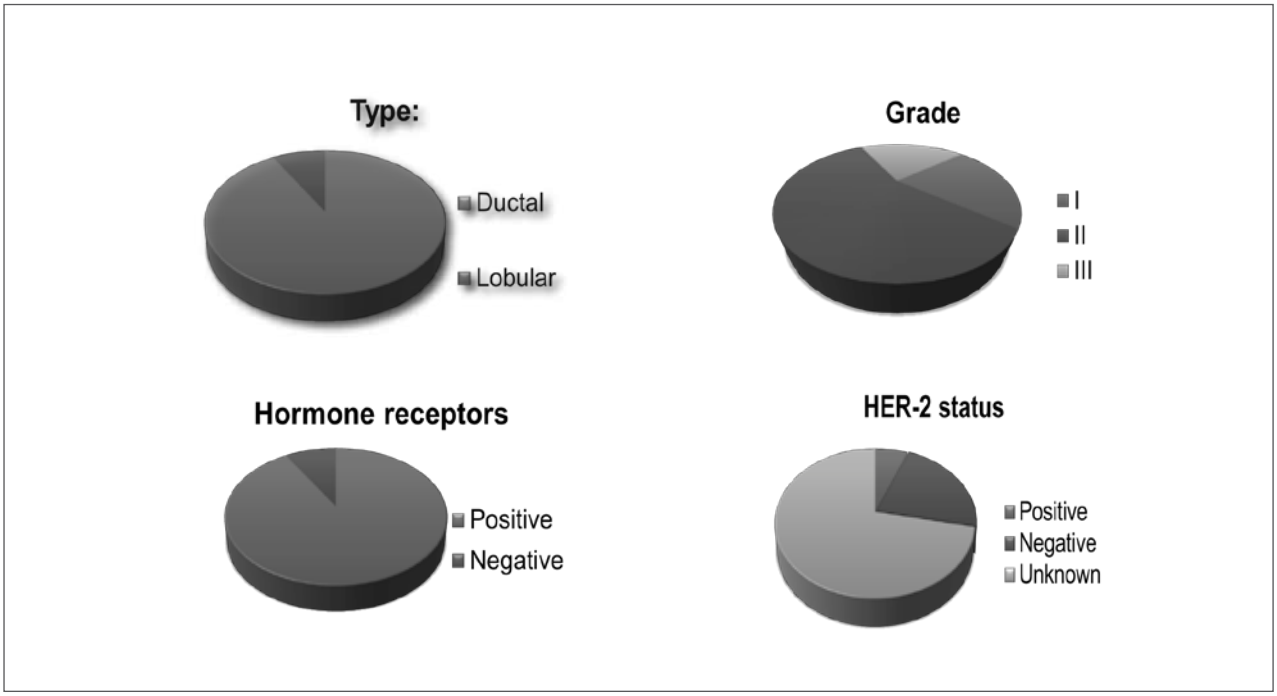


Figure 1. Tumour biology characterisation.

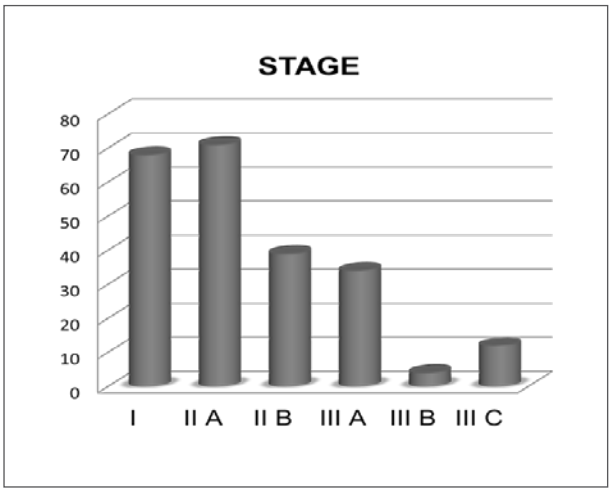


Figure 2. Breast cancer staging at diagnosis.

by the end of 2005 in our institution. Therefore, the HER-2 status was positive in 10 patients, negative in 36 and unknown in the majority (177). The most frequent stage was stage II (110 patients).

The restaging exams diagnosed metastatic disease in 8 (3.5%) patients: 3 patients in stage II (2.7% in 110 patients) and 5 in stage III (10% in 50 patients).

In this group of the eight asymptomatic patients with metastasis, the more frequent histological type was invasive ductal carcinoma (75%), grade II (75%). Most of the patients had positive hormone receptors (87.5%). The HER-2 status was negative in four patients (50%), positive in one (12.5%) and unknown in three (37.5%).

Of the eight patients, 50% had bone metastasis, 30% liver metastasis and 20% lung metastasis.

BS was carried out in 201 patients, LUS in 188 and CXR in 190.

STAGE	N	METASTIZED	% DETECTION
I	68	0	**0**
IIA	71	1	**1,4**
IIB	39	2	**5,12**
IIIA	34	3	**8,9**
IIIB	4	0	**0**
IIIC	12	2	**16,6**

→ Stage II 2,7 %

→ Stage III 10 %

Figure 3. Rate of detection of metastatic disease in restaging exams.

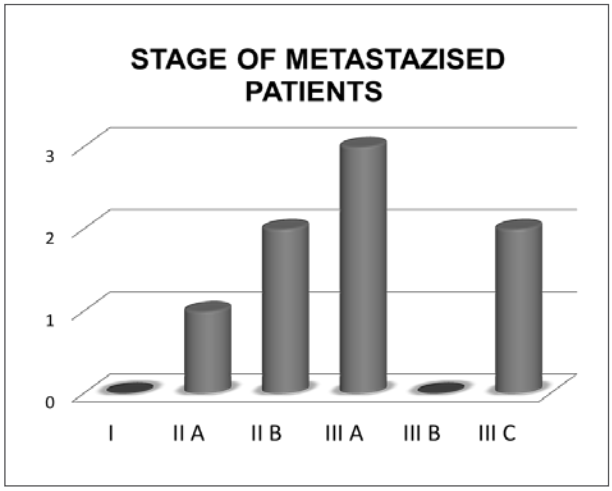


Figure 4. Initial stage of patients with asymptomatic metastasis in 5-year restaging follow-up tests.

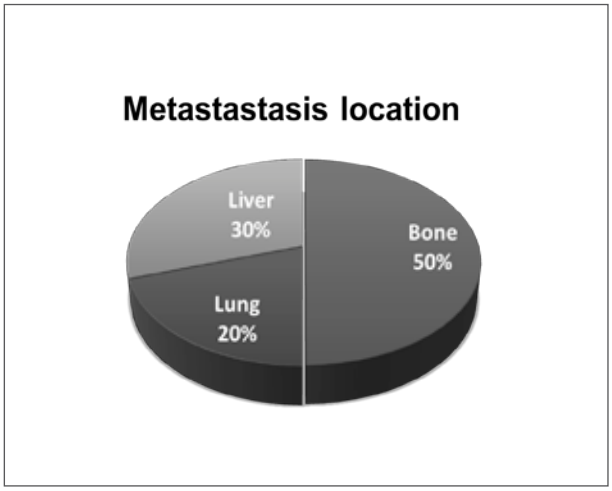


Figure 5. Metastasis location in 5-year restaging exams.

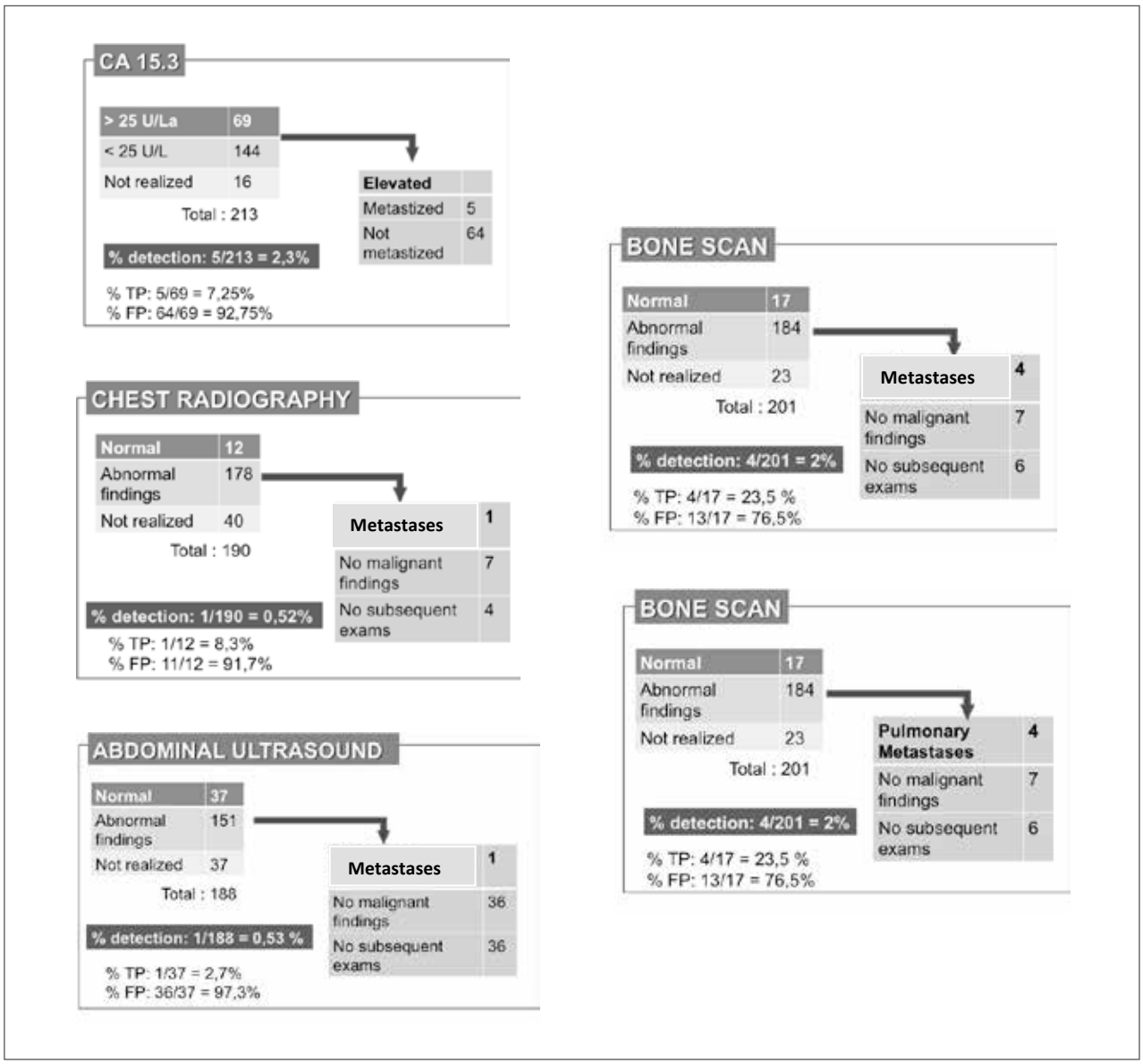


Figure 6. Restaging testscharacterisation and percentage of metastasis detection.

BS detected bone metastases in 2% of patients, LUS detected liver metastases in 0.53% and CXR detected lung metastases in 0.52%.

The tumour marker Ca15-3 was tested in 213 patients (93.4%). Elevation of Ca 15.3 was documented in 19% of the cases but it only had a true positive rate of 7.25%. Most of the patients that had an elevated Ca15-3 were not metastasised. The tumour marker recorded a metastasis detection rate of greater than 2%, but with 15% false positives.

The median time of follow-up after the diagnosis of metastasised disease was 25.2 months.

Discussion

Currently, we have several studies that show benefit with extended hormone therapy until until 10 years of treatment, either with tamoxifen or an aromatase inhibitor. This means that most patients will be followed in cancer centres for a longer period of time. This new scenario represents a challenge to cancer centres that have become overcrowded.

Stage I and II breast cancer, particularly luminal subtypes, have risk of recurrence after 5 years (4%–10%) and although inferior, they can recur after 10 or more years.[1,8,10] Patients should also be followed-up to detect new primary tumours of the breast (or another location) and late adverse events of adjuvant treatment.[6,8,19]

National health systems differ from country to country. In some countries, breast cancer patients are followed-up by their primary care physician; in others, (e.g. Portugal) cancer care and follow-up are still based in cancer centers.[15-17, 19]

Although we know that the rate of metastases diagnosis was very small in the initial staging work-up of breast cancer patients, our cancer centre performs a restaging evaluation prior to discharge (CXR, LUS and BS). The results are consistent with initial staging for early breast cancer.[1,2,18]

It is still possible to argue that data from the initial staging work-up is old data, and that nowadays, with more modern exams (e.g. CT or positron emission tomography [PET]-CT), it is possible to have a greater detection rate.[20] It has been suggested that PET-CT should be recommended for patients with tumours at stage IIB or higher, due to detection of additional lymph node metastases and the impact of future prognosis.[18] Numerous studies have been conducted concerning the prognostic factors of the PET-CT, but they yielded discrepant results, partly due to heterogeneous groups of patients. However, the impact on overall survival or quality of life is still unknown.[21-26]

In our retrospective study, after 5 years of follow-up, in stages II and III the prevalence of metastatic disease with conventional work-up was greater than 1%. BS had a significant detection rate (2%). The detection rate of the tumour marker CA15-3 has to be interpreted with caution because, although this rate is significant (2.3%), the false positive rate is high, especially in some subgroups of patients.[27,28]

We believe that this finding can support the evidence to do this routinely, but these findings should be better analysed in a trial, with a larger sample of patients, particularly of stage II and III.

The concept that the benefit of more extensive initial staging can be more useful in more aggressive subtypes or locally advanced tumours does not apply at the time of discharge because usually these patients have recurrences earlier.[29,30]

Many of the patients analysed in our sample did not have an HER-2 or Ki-67 evaluation, and none had Oncotype DX®, MammaPrint®, PAM 50 (Prosigna®) or any other genetic tools. However, these new tools may, in the near future, help in deciding not only between chemotherapy versus endocrine treatment, but also the duration of endocrine treatment and follow-up. Greater personalised medicine is needed and precision medicine should be more relevant than it is today.[31-35]

The issue of discharge work-up also has the purpose of avoiding legal problems and improving care for cancer patients, because it allows us to make the discharge a friendlier experience for the patient. The psychological impact and quality of life associated with this discharge work-up also should be evaluated in a future clinical trial.

Long-term adverse events, particularly those resulting from cumulative use of harmful radiation is of great importance. A prospective clinical trial comparing different discharge work-up strategies (e.g. driven by symptoms and signals on physical examination; minimal discharge follow-up for all patients; CT or PET-CT) is the better way to answer this question. Survival, quality of life and loss of work days are all important aspects to analyse.

Conclusions

These findings indicate that a complete restaging work-up to detect metastases in asymptomatic patients 5 years after the diagnosis and treatment of breast cancer seems unnecessary in patients in stage I. In stages II and III, the prevalence of metastatic disease with these exams was superior to 1%, which—according to the detection rate is considered as significant—indicates the benefit in doing it routinely. The only restaging exam that had a significant detection rate (2%) was the BS. The detection rate of the tumour marker has to be interpreted with caution, because although this rate is significant (2.3%), the rate of false positives is elevated. To consolidate these findings/conclusions, a large sample in stage II and III should be evaluated. On other hand, these patients should be characterised by their HER-2 status, Ki-67 or even multigene assay to predict the recurrence of tamoxifen-treated, node-negative breast cancer, which could likely improve our conclusions, allowing us a better stratification of risk subgroups.

Clinical trials comparing CT scan, PET-CT and genomic tools are needed. With increasing health costs, questions about the initial and particularly the discharge workup should be addressed in prospective studies. Legal considerations, long-term

adverse events and improvement in care for cancer patients also should be taken into account.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

References

1. http://eco.iarc.fr/EUCAN/CancerOneaspx?Cancer=46&Gender=2#block-table-f (Accessed 20 September 2018.)
2. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 2015;385:977-1010.
3. RORENO. Registo Oncológico Nacional 2010. Instituto Português de Oncologia do Porto Francisco Gentil - EPE, ed. Porto, 2016.
4. Giordano SH, Elias AD, Gradishar WJ. NCCN Guidelines Updates: Breast Cancer. JNCCN. 2018;16:605-610.
5. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)dagger. Ann Oncol. 2018;29:1634-1657.
6. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 3.2013. https://www.NCCN.com (Accessed 29 July 2018.)
7. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies–improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015;26:1533-1546.
8. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol.2015;26 Suppl. 5:v8-30.
9. Myers RE, Johnston M, Pritchard K, Levine M, Oliver T, Breast Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines I. Baseline staging tests in primary breast cancer: a practice guideline. CMAJ. 2001;164:1439-1444.
10. Penault-Llorca F, Coeffic D, Delozier T, et al. Node negative breast cancer. Beyond international consensus: a pragmatic approach. Bulletin du cancer. 2011;98:807-825.
11. Carlson RW, McCormick B. Update: NCCN breast cancer Clinical Practice Guidelines. JNCCN. 2005;3 Suppl 1:S7-11.
12. Carlson RW, Allred DC, Anderson BO, et al. Invasive breast cancer. JNCCN. 2011;9:136-222.
13. Khatcheressian JL, Wolff AC, Smith TJ, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. Clin Oncol. 2006;24:5091-5097.
14. Davis C, Williams P, Redman S. Early discharge following breast surgery: assessing care, support, and informational needs of women with early breast cancer in Australia. Aust N Z J Surg. 2000;70:569-572.
15. Railton C, Lupichuk S, McCormick J, et al. Discharge to primary care for survivorship follow-up: how are patients with early-stage breast cancer faring? JNCCN. 2015;13:762-771.
16. Paswan SS, Kataria K, Parshad R, Srivastava A, Seenu V, Mishra B. Feasibility of fast track discharge in breast cancer patients undergoing definitive surgery and impact on quality of life: a prospective study from tertiary care center in India. J Surg Oncol. 2015;111:265-269.
17. Roorda C, Berendsen AJ, Haverkamp M, van der Meer K, de Bock GH. Discharge of breast cancer patients to primary care at the end of hospital follow-up: a cross-sectional survey. Eur J Canc. 2013;49:1836-1844.
18. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17:1471-1474.
19. Barnadas A, Algara M, Cordoba O, et al. Recommendations for the follow-up care of female breast cancer survivors: a guideline of the Spanish Society of Medical Oncology (SEOM), Spanish Society of General Medicine (SEMERGEN), Spanish Society for Family and Community Medicine (SEMFYC), Spanish Society for General and Family Physicians (SEMG), Spanish Society of Obstetrics and Gynecology (SEGO), Spanish Society of Radiation Oncology (SEOR), Spanish Society of Senology and Breast Pathology (SESPM), and Spanish Society of Cardiology (SEC). Clin Transl Oncol. 2018;20:687-694.
20. Cooper KL, Meng Y, Harnan S, et al. Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: systematic review and economic evaluation. Health Technol Assess. 2011;15:iii-iv, 1-134.
21. Jodlowska E, Czepczynski R, Czarnywojtek A, et al. The application of positron emission tomography (PET/CT) in diagnosis of breast cancer. Part II. Diagnosis after treatment initiation, future perspectives. Contemp Oncol (Pozn). 2016;20:205-209.
22. Jodlowska E, Czepczynski R, Wyszomirska A, Jarzabek G, Kedzia W, Ruchala M. Application of positron emission tomography (PET/CT) in diagnosis of breast cancer. Part I. Diagnosis of breast cancer prior to treatment. Contemp Oncol (Pozn). 2016;20:8-12.
23. Robertson IJ, Hand F, Kell MR. FDG-PET/CT in the staging of local/regional metastases in breast cancer. Breast. 2011;20:491-494.
24. Cooper KL, Harnan S, Meng Y, et al. Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: A systematic review and meta-analysis. Eur J Surg Oncol. 2011;37:187-198.
25. Meng Y, Ward S, Cooper K, Harnan S, Wyld L. Cost-effectiveness of MRI and PET imaging for the evaluation of axillary

lymph node metastases in early stage breast cancer. Eur J Surg Oncol. 2011;37:40-46.

26. Garami Z, Hascsi Z, Varga J, et al. The value of 18-FDG PET/CT in early-stage breast cancer compared to traditional diagnostic modalities with an emphasis on changes in disease stage designation and treatment plan. Eur J Surg Oncol. 2012;38:31-37.

27. Bast RC, Jr., Ravdin P, Hayes DF, et al. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol. 2001;19:1865-1878.

28. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007;25:5287-5312.

29. Devita VT, Jr. Breast cancer screening and mortality. Nat Rev Clin Oncol. 2010;7:65.

30. Carey L, Winer E, Viale G, Cameron D, Gianni L. Triple--negative breast cancer: disease entity or title of convenience? Nat Rev Clin Oncol. 2010;7:683-692.

31. Kirk R. Risk factors. Oncotype DX assay predicts local recurrence in breast cancer. Nat Rev Clin Oncol. 2010;7:300.

32. Oakman C, Santarpia L, Di Leo A. Breast cancer assessment tools and optimizing adjuvant therapy. Nat Rev Clin Oncol. 2010;7:725-732.

33. Fumagalli D, Sotiriou C. Treatment of pT1N0 breast cancer: multigene predictors to assess risk of relapse. Ann Oncol. 2010;21 Suppl 7:vii103-106.

34. Vieira AF, Schmitt F. An update on breast cancer multigene prognostic tests-emergent clinical biomarkers. Front Med (Lausanne). 2018;5:248.

35. Bhutiani N, Egger ME, Ajkay N, Scoggins CR, Martin RC, 2nd, McMasters KM. Multigene signature panels and breast cancer therapy: patterns of use and impact on clinical decision making. J Am Coll Surg. 2018;226:406-412 e401.

Artigo de investigação original

Cuidados paliativos na neoplasia do pulmão – Realidade de uma equipa de Cuidados Paliativos

Palliative care in lung cancer – The reality of a palliative care team

Autor:
Ana Isabel Lopes, Paula Marques Ferreira, Céu Rocha, Hugo M Oliveira

Afiliação:
Ana Isabel Lopes
Interna de Formação Específica de Medicina Interna, Serviço de Medicina Interna, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal

Paula Marques Ferreira
Interna de Formação Específica de Medicina Interna, Serviço de Medicina Interna, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal

Céu Rocha
Equipa de Cuidados Paliativos da Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal

Hugo M Oliveira
Equipa de Cuidados Paliativos da Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal
Assistente Hospitalar de Medicina Interna, Serviço de Medicina Interna, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal

Conflitos de interesse:
None

Financiamento:
Trabalho realizado sem necessidade de financiamento

Autor para correspondência:
Ana Isabel Lopes
Morada: Serviço de Medicina Interna, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal
Email: ana_spol18@hotmail.com

Resumo:

Objetivos: Caraterizar os doentes com neoplasia pulmonar referenciados a uma equipa de cuidados paliativos e analisar as características dos que desenvolveram emergências oncológicas e dos que necessitaram de medidas paliativas complexas.

Métodos: Análise de coorte retrospetiva avaliando todos os doentes com neoplasia do pulmão referenciados a cuidados paliativos.

Resultados: A maioria de doentes apresentava carcinoma de não pequenas células em estadio avançado e mais de metade estava sob tratamento ativo. Os doentes foram referenciados principalmente por dor e dispneia. Após avaliação a mediana de sobrevida foi de 8 semanas. Dezasseis por cento dos doentes apresentaram uma emergência oncológica, sendo a síndrome da veia cava superior a emergência mais comum (40,0%). Uma percentagem significativa (41,6%) necessitou de medidas paliativas complexas, sendo estes doentes mais precocemente referenciados para cuidados paliativos.

Conclusões: A crescente incidência da neoplasia do pulmão e o impacto da sintomatologia associada implica uma integração mais precoce dos cuidados paliativos. No estudo apresentado a mediana de sobrevida após a referenciação é reduzida e reforça a necessidade duma referenciação mais atempada. Contudo são necessários mais estudos para colmatar a informação nesta área.

Palavras-chave: Cuidados paliativos, Neoplasia pulmonar, Dispneia, Dor, Emergências.

Abstract:

Objectives: *Characterize the patients with lung cancer referred to a palliative care team and analyze the characteristics of patients who developed oncological emergencies and patients who needed complex palliative measures.*

Methods: *Retrospective cohort analysis, assessing all patients with lung cancer referred to palliative care.*

Results: *Most patients had advanced non-small cell carcinoma and were under active treatment. The patients were mainly referred by pain and dyspnea, with a median survival of 8 weeks. Sixteen percent of patients experienced a cancer emergency during the course of their illness and the most common emergency was vena cava syndrome (40.0%). An important percentage of patients needed complex palliative measures and were earlier referred to our team.*

Conclusions: *The increasing incidence of lung cancer and the impact of the associated symptomatology should lead to the promotion of an early integration of*

palliative care. In the present study, the median survival after referral is reduced, reinforcing the need for an early integration. Because of the poor information on this subject, further studies are needed.

Keywords: *Palliative care, Lung neoplasms, Dyspnea, Pain, Emergencies.*

Introdução

A incidência da neoplasia do pulmão tem apresentado uma escalada a nível mundial, mantendo-se líder da mortalidade por cancro[1]. A taxa de incidência de cancro do pulmão varia geograficamente refletindo as diferenças nos hábitos tabágicos e na poluição atmosférica das diferentes regiões[1, 2]. Em Portugal, segundo a Direção Geral de Saúde, a incidência em 2010 foi de 35.8/100.000 habitantes[3].

A maioria dos doentes são diagnosticados em fases avançadas, em que a taxa de sobrevida aos 5 anos é baixa, e apenas 20% são diagnosticados em estadio cirúrgico[4]. Apesar dos tratamentos atuais com intuito curativo, a recidiva é frequente e os efeitos adversos das terapêuticas afetam significativamente a qualidade de vida dos doentes[5, 6].

Na doença avançada os sintomas apresentados têm grande impacto. Os estudos mostram que os sintomas mais frequentes são fadiga e anorexia (98%), seguido de dispneia, tosse e dor (em 94%, 93% e 90% respetivamente)[7]. Os cuidados paliativos assumem um papel fulcral na gestão destes doentes, não só para controlo dos sintomas físicos, psicológicos e sofrimento existencial, como também para facilitar a comunicação com os doentes e seus familiares. Assim, os cuidados paliativos contribuem para uma melhoria da qualidade de vida e ainda para o aumento da sobrevida[5, 8].

A Equipa de Cuidados Paliativos da Unidade Local de Saúde de Matosinhos (ECP-USLM), na perspetiva atual dos cuidados paliativos, ambiciona uma integração precoce de medidas paliativas ao longo do percurso de doença. A ECP-ULSM dispõe de valência intra-hospitalar e domiciliária, o que permite uma avaliação do doente em ambos os regimes, ajustando ao *status* funcional do doente. Este trabalho teve como objetivos: caraterizar os doentes com neoplasia pulmonar referenciados à ECP-USLM e, destes, analisar os que desenvolveram emergências oncológicas e também os que necessitaram de medidas paliativas complexas.

Métodos

Realizado um estudo de coorte retrospetiva que incluiu todos os doentes com neoplasia do pulmão referenciados à ECP-ULSM, entre 1 de janeiro de 2017 e 31 de dezembro de 2018. A informação necessária foi obtida por consulta do processo clínico eletrónico (PCE), sendo registados dados demográficos (idade à referenciação e sexo) e clínicos (tempo de doença, diferencial entre data de diagnóstico e referenciação à ECP-ULSM, subtipo histológico, estadio à referenciação, presença e local de metastização, tratamento ativo de quimioterapia, motivo de referenciação e sobrevida após referenciação). Foi também avaliado o desenvolvimento de emergências oncológicas ou a necessidade de medidas paliativas complexas. Consideraram-se como emergências oncológicas: compressão medular, hipercalcemia maligna, neutropenia febril, síndrome da veia cava superior e síndrome de lise tumoral. Definiu-se como medidas paliativas complexas: a necessidade de implementação e manutenção de perfusão sistémica de opióide por dor e/ou dispneia; ou a necessidade de sedação paliativa (contínua ou intermitente) por dispneia refratária ou inquietação.

O tratamento estatístico dos dados foi realizado através do programa IBM SPSS®, versão 20. As variáveis categóricas (sexo, motivo de referenciação, histologia, tratamento com quimioterapia, metastização, emergência oncológica, cuidados paliativos complexos e mortalidade) são apresentadas como frequências e percentagens e as variáveis contínuas (idade, tempo de doença, diferencial entre diagnóstico e referenciação e sobrevida após avaliação) como médias e desvio padrão ou mediana e intervalos inter-quartil (IIQ), na presença ou ausência de distribuição normal, respetivamente. A presença de associação entre variáveis categóricas foi analisada através do teste qui-quadrado, e foi usado o teste *t* de *student* ou o Mann-Whitney para análise de variáveis contínuas seguindo ou não a distribuição normal, respetivamente. Foi considerada uma diferença estatisticamente significativa sempre que o valor de prova (valor-p, p) não excedesse o nível de significância de 5% ($p < 0,05$).

O estudo foi realizado em linha com as recomendações da Declaração de Helsínquia da World Medical Association.

Resultados

1. Caraterização da população total (Tabela 1)

No período em análise foram referenciados à ECP-ULSM 125 doentes, tendo sido todos incluídos no estudo. A maioria (80,0%) eram do sexo masculino, e a média de idades foi de 68,5 ± 11,4 anos (Figura 1). A caraterização da população está apresentada na Tabela 1.

Foi documentada uma grande variabilidade no tempo até referenciação à ECP-ULSM, com mediana de 12 semanas, mas valores entre as 3 e as 44 semanas.

A primeira avaliação do doente pela equipa foi realizada, em 90,4% dos casos (n = 113), em ambiente hospitalar (internamento ou consulta externa), sendo os restantes (9,6%) avaliados pela primeira vez no domicílio.

Setenta e quatro por cento dos doentes apresentavam carcinoma de não pequenas células e 20,8% carcinoma de pequenas células. Os 4,8% restantes não dispunham de diagnóstico histológico, assumindo-se o diagnóstico de neoplasia pulmonar com base em parâmetros clínicos e imagiológicos. À data de referenciação 80,0% encontravam-se em estadio IV.

Encontravam-se sob tratamento ativo 59,2% dos doentes e destes, 66,2% ainda estavam em primeira linha de quimioterapia.

A dor, presente em 28,8% dos casos, e a dispneia, presente em 25,6%, corresponderam aos principais motivos de referenciação. A tosse revelou-se uma causa rara de referenciação (Tabela 1).

Após avaliação pela ECP-ULSM a mediana de sobrevida dos doentes foi de 8 semanas com IQR 13 (Q_1 = 3 e Q_3 = 16) sendo a taxa de mortalidade, 3 meses após o período em análise, de 95,2% (n = 119).

Tabela 1. Caraterização da população total.

Idade (anos)	
Média	68,5
Desvio padrão	±11,4
Género, n (%)	-
Masculino	100 (80,0%)
Feminino	25 (20,0%)
Média idade por género, anos	-
Masculino	68,3
Feminio	69,4
Tempo de doença (semanas)	
Mediana	28,0
Intervalo interquartil (iiq)	53
Q_1	10
Q_3	63
Diferencial entre data de diagnóstico e referenciação (semanas)	
Mediana	12,0
Intervalo interquartil (iqr)	41
Q_1	3
Q_3	44
Estadio à data de referenciação, n (%)	
I	1 (0,8%)
Ii	7 (5,6%)
Iii	16 (12,8%)
Iv	100 (80,0%)
Metastização à data de referenciação, n (%)	
Glândula suprarrenal	107 (85,6%)
Ganglionar	105 (84%)
Cérebro	100 (80%)
Figado	99 (79,2%)
Pulmão contralateral	99 (79,2%)
Osso	75 (60%)

Tabela 1. Caraterização da população total. ***Continuação***	
Motivo de referenciação, n (%)	
Dor	36 (28,8%)
Dispneia	32 (25,6%)
Caquexia	17 (13,6%)
Tosse	4 (3,2%)
Hemoptise	1 (0,8%)
Outros	44 (35,2%)

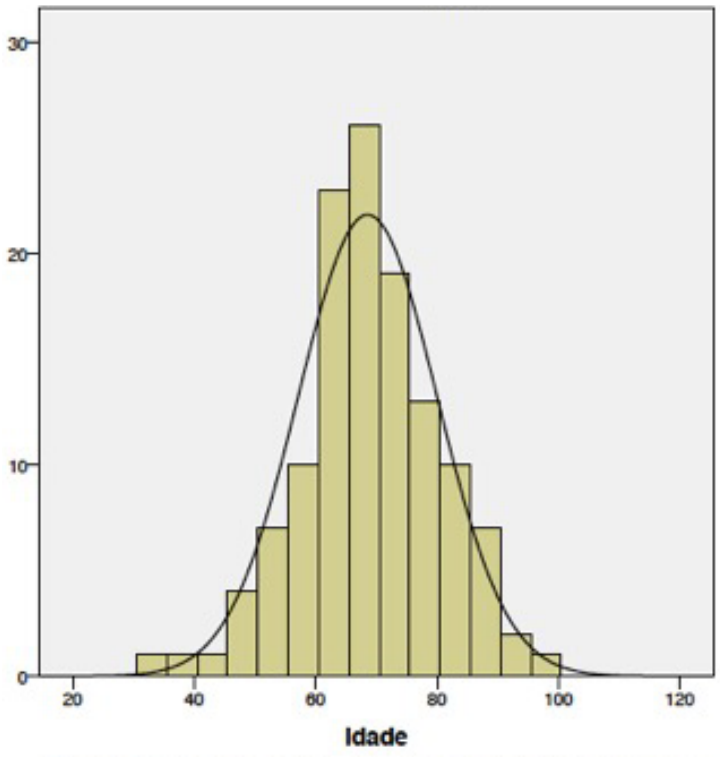


Figura 1. Distribuição dos doentes referenciados de acordo com idade (em anos).

2. Emergências oncológicas (Tabela 2)

Dos doentes referenciados à ECP-ULSM, 16,0% (n = 20) apresentaram uma emergência oncológica. A síndrome da veia cava superior foi a mais comum (40,0%), seguida, em percentagens iguais (20,0%), pela compressão medular, hipercalcemia maligna e neutropenia febril.

Estes doentes apresentavam tendencialmente uma idade mais jovem (64,7 vs. 69,3 anos), menor tempo de evolução de doença e foram mais precocemente referenciados à ECP-ULSM, em relação aos doentes sem emergência oncológica; contudo, não foi documentada uma diferença estatisticamente significativa (p = 0,069, p = 0,251, p = 0,313, respetivamente).

Verificou-se uma associação entre a ausência de emergências oncológicas e o carcinoma de não pequenas células (p = 0,026) e a existência de metastização pulmonar contralateral (p = 0,045) (Tabela 2).

A sobrevida desde a referenciação à ECP-ULSM documentada nesta população foi sobreponível à população sem emergências oncológicas (64,8 vs. 62,4 semanas).

Tabela 2. Análise comparativa da população com emergências oncológicas *vs.* Sem emergência oncológica.

Categoria	Presença emergência oncológica	Ausência emergência oncológica	P
Idade (anos)			
	64,7	69,3	0,069
Género, n (%)			
Masculino	19 (95,0%)	81 (77,1%)	0,054
Feminino	1 (5,0%)	24 (22,9%)	
Tempo de doença (semanas)			
Mean rank	54,5	64,6	0,251
Tempo de doença na referenciação (semanas)			
Mean rank	55,5	64,4	0,313
Sobrevida (semanas)			
Mean rank	64,8	62,4	0,800
Histologia, n (%)			
Pequenas células	8 (42,1%)	18 (18,0%)	0,026
Não pequenas células	11 (57,9%)	82 (82,0%)	
Doença à distância			
Pulmonar contralateral	1 (3,8%)	25 (96,2%)	0,045
Ganglionar	4 (20,0%)	16 (80,0%)	0,401
Glândula suprarrenal	5 (27,8%)	13 (72,2%)	0,132
Osso	5 (10,0%)	45 (90,0%)	0,105
Cérebro	1 (4,0%)	24 (96,0%)	0,054
Figado	4 (15,4%)	22 (84,6%)	0,596
Motivo de referenciação, n (%)			
Dor	7 (19,4%)	29 (80,6%)	0,337
Dispneia	3 (9,4%)	29 (90,6%)	0,184
Caquexia	3 (17,6%)	14 (82,4%)	0,538
Tosse	0 (0,0%)	4 (100,0%)	0,493
Hemoptise	0 (0,0%)	1 (100,0%)	0,840
Outros	7 (15,9%)	37 (84,1%)	0,599

3. Medidas paliativas complexas (Tabela 3)

Uma percentagem significativa dos doentes (41,6%, n = 52) necessitou de medidas paliativas complexas, nomeadamente perfusão sistémica de opióides para controlo de dor e/ou dispneia em 73,1% (n = 38), sedação paliativa em 19,2% (n = 10) ou de ambos em 7,7% (n = 4). A Tabela 3 apresenta os dados referentes a este grupo de doentes.

Estes doentes eram tendencialmente mais jovens (66,8 vs. 69,8 anos, p = 0,141), apresentavam menos tempo de doença (51,1 vs. 71,5 semanas, p = 0,002) e eram mais precocemente referenciados à ECP-ULSM (52,1 vs. 70,7 semanas, p = 0,005).

Nesta população também se verificou uma associação entre a necessidade de medidas paliativas complexas e a existência de dor (p = 0,035).

Os doentes com necessidade de medidas paliativas complexas tiveram uma sobrevida, desde a referenciação à equipa, significativamente inferior à restante população em análise (52,6 vs. 70,3 semanas, p = 0,007).

Tabela 3. Análise comparativa da população com necessidade de medidas paliativas complexas vs. sem necessidade.

Categoria	Cuidados complexos	Sem cuidados complexos	P
Género, n (%)			
Masculino	44 (84,6%)	56 (76,7%)	0,195
Feminino	8 (15,4%)	17 (23,3%)	
Média de idade (anos)			
	66,8	69,8	0,141
Tempo de doença (semanas)			
Mean rank	51,1	71,5	0,002
Tempo de doença na referenciação (semanas)			
Mean rank	52,1	70,7	0,005
Sobrevida (semanas)			
Mean rank	52,6	70,3	0,007
Histologia, n (%)			
Pequenas células	10 (38,5%)	16 (61,5%)	0,466
Não pequenas células	39 (41,9%)	54 (58,1%)	
Doença à distância			
Pulmonar contralateral	12 (46,2%)	14 (53,8%)	0,378
Ganglionar	11 (55,0%)	9 (45,0%)	0,141
Glândula suprarrenal	7 (38,9%)	11 (61,1%)	0,507
Osso	22 (44,0%)	28 (56,0%)	0,397
Cérebro	12 (48,0%)	13 (52,0%)	0,307
Figado	12 (46,2%)	14 (53,8%)	0,378
Motivo de referenciação, n (%)			
Dor	20 (55,6%)	16 (44,4%)	0,035
Dispneia	14 (43,7%)	18 (56,3%)	0,467
Caquexia	5 (29,4%)	12 (70,6%)	0,204
Tosse	2 (50,0%)	2 (50,0%)	0,554
Hemoptise	0 (0,0%)	1 (100,0%)	0,584
Outros	16 (36,4%)	28 (63,6%)	0,247

Discussão

Este é um estudo pioneiro não só na caraterização de uma população de doentes com neoplasia do pulmão referenciados a uma equipa de cuidados paliativos, como também na análise de duas subpopulações que durante o percurso de doença apresentam intercorrências significativas (doentes com emergências oncológicas e doentes que necessitaram de medidas paliativas complexas).

Na população total analisada (doentes referenciados por neoplasia do pulmão à ESCP) a neoplasia do pulmão foi mais frequente no sexo masculino; a maioria teve diagnóstico histológico de carcinoma de não pequenas células, indo de encontro aos valores encontrados na literatura, embora com uma média

de idades inferior[9,10]. Os estudos mostram que, num elevado número de casos, o diagnóstico é feito em estadios avançados de doença e o objetivo do tratamento é melhorar a sobrevida e reduzir os efeitos adversos da doença[10]. Os resultados da nossa unidade hospitalar revelam que 80,0% dos doentes referenciados encontram-se em estadio IV. Contudo, importa assinalar que este valor diz respeito apenas aos doentes referenciados à ECP-ULSM e não à totalidade dos doentes com o diagnóstico de neoplasia pulmonar na nossa instituição de saúde.

À semelhança dos estudos existentes, a maioria dos doentes foram referenciados por dor e dispneia[5] e, em menor percentagem, por caquexia, tosse e hemoptises.

Verificou-se que, nesta população de doentes referenciados à ESCP com neoplasia do pulmão, mais de 50% dos doentes foram referenciados à equipa ainda sob tratamento ativo e sob quimioterapia de primeira linha, o que vai de encontro às orientações do *National Institute for Clinical Excellence*, que favorece uma integração precoce de cuidados[11]. Contudo, importa destacar a grande variabilidade no tempo até referenciação, com doentes a serem referenciados com mais de 40 semanas após o diagnóstico e uma mediana de sobrevida após referenciação de 8 semanas, um tempo reduzido para conseguir abranger com sucesso as várias valências de atuação dos cuidados paliativos.

A taxa de mortalidade da neoplasia do pulmão é influenciada pelo estadio de doença ao diagnóstico[3]. A mortalidade global estimada no mundo em 2018 foi de 1,76 milhões (dados da OMS)[12]. De acordo com estes dados, e sabendo que a população deste estudo tem maioritariamente doença avançada, a taxa de mortalidade cumulativa nos 27 meses de análise foi de 95,2%.

Ao longo do percurso da doença, 16,0% dos doentes apresentaram pelo menos uma emergência oncológica, valor que empiricamente acreditávamos ser mais elevado, mas não possível de validar, dada a ausência de estudos sobre esta temática nos doentes com neoplasia do pulmão. A síndrome da veia cava superior foi a emergência mais frequente, o que está de acordo com a literatura, que mostra que a neoplasia pulmonar é a responsável por 60-80% dos casos desta síndrome[13,14]. O carcinoma de não pequenas células e a presença de metastização pulmonar contralateral estavam associados a um menor número de emergências oncológicas. Apesar de não se documentarem resultados com significância estatística, os doentes com emergências oncológicas foram mais precocemente referenciados à ECP-ULSM, o que sugere que o aparecimento desta intercorrência é sinal de alerta para referenciação a cuidados paliativos.

São múltiplos os sintomas que os doentes podem ter, quer na dependência do tumor primário quer da sua metastização, sendo por vezes necessárias várias estratégias terapêuticas para atingir o controlo sintomático. Uma percentagem não desprezível dos doentes com neoplasia do pulmão referenciados à ECP-ULSM (41,6%) teve necessidade de medidas paliativas complexas. A dor foi o único fator associado à necessidade de medidas paliativas complexas. Os doentes com dor constituíam um subgrupo tendencialmente mais jovem e que foram, de uma forma estatisticamente significativa, referenciados mais precocemente à ECP-ULSM o que parece indicar uma maior sensibilidade, por parte das outras especialidades, para solicitar a colaboração dos cuidados paliativos perante sintomas de difícil gestão.

Embora se saiba que uma referenciação precoce tem impacto na qualidade de vida dos doentes, pelos benefícios de um acompanhamento por uma equipa de cuidados paliativos, uma das limitações deste estudo prende-se com a ausência de dados relativos à qualidade de vida dos doentes.

Conclusões

A crescente incidência da neoplasia do pulmão, a gravidade dos sintomas que surgem nas fases avançada da doença e o impacto que a mesma condiciona nos sistemas de saúde devem levar à implementação de uma integração precoce de cuidados entre as várias especialidades médicas que acompanham estes doentes: pneumologia, oncologia, cirurgia torácica e cuidados paliativos. Esta abordagem permite uma adequada gestão de recursos e a prestação de um apoio conjunto ao doente, atendendo não só às suas necessidades físicas, mas também psicológicas e sociofamiliares. No estudo apresentado existe uma percentagem considerável de doentes referenciados ainda sob tratamento activo, mas a mediana de sobrevida após referenciação é reduzida, um indício da necessidade de iniciar o processo de referenciação de forma mais precoce.

Com este estudo conseguimos não só avaliar as caraterísticas populacionais dos doentes com neoplasia pulmonar em seguimento por uma equipa de cuidados paliativos em Portugal, como também perceber que alguns sinais, como o aparecimento de emergências oncológicas e a dor, parecem desencadear a referenciação a cuidados paliativos.

A escassez de informação sobre esta temática força a necessidade de mais estudos que possam validar os achados encontrados pela nossa Equipa de Cuidados Paliativos e contribuir com novos dados.

Referências

1. de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. Transl Lung Cancer Res. 2018;7(3):220-233.
2. Torre LA, Siegel RL, Jemal A. Lung Cancer Statistics. Adv Exp Med Biol. 2016;893:1-19.
3. Sotto-Mayor R. Lung Cancer Mortality. Acta Med Port. 2014;27(1):9-11.
4. Parente B, Queiroga H, Teixeira E, et al. Estudo epidemiológico do cancro do pulmão em Portugal nos anos de 2000/2002. Rev Port Pneumol. 2007;13(2):255-265.
5. Ferrell B, Koczywas M, Grannis F, Harrington A. Palliative care in lung cancer. Surg Clin North Am. 2011;91(2):403-ix.
6. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of patients with lung cancer. Onco Targets Ther. 2016;9:1023-1028.
7. Iyer S, Taylor-Stokes G, Roughley A. Symptom burden and quality of life in advanced non-small cell lung cancer patients in France and Germany. Lung Cancer. 2013;81(2):288-293.
8. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. The New England journal of medicine. 2010;363(8):733-742.
9. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med. 2011;32(4):605-644.
10. Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. Transl Lung Cancer Res. 2016;5(3):288-300.
11. National Institute for Clinical Excellence. Lung cancer: diagnosis and management. Março 2019. Disponível em: https://www.nice.org.uk/guidance.
12. World Health Organization, International Agency for Research on Cancer. Globocan 2018: Lung Cancer. Março, 2019. Disponível em: http://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf.
13. De Potter B, Huyskens J, Hiddinga B, et al. Imaging of urgencies and emergencies in the lung cancer patient. Insights Imaging. 2018;9(4):463-476.
14. Wudel LJ Jr, Nesbitt JC. Superior vena cava syndrome. Curr Treat Options Oncol. 2001;2:77-91.

Artigo de investigação original

Os registos de dor são fatores preditivos de morte em doentes hospitalizados

Pain records are predictors of death in hospitalised cancer patients

Autores:
Cláudia Margarida Pereira Vieira[1,2,3], **Rosa Maria Fragoso**[1,4], **Jorge Freitas**[1], **Nelson Domingues**[1], **Deolinda Pereira**[1], **Rui Medeiros**[2,3,5,6]

Afiliação:
[1]Medical Oncology Department, Instituto Português de Oncologia do Porto Francisco Gentil (IPO-PORTO), Porto, Portugal
[2]Research Centre - Molecular Oncology Group-CI, Instituto Português de Oncologia do Porto Francisco Gentil (IPO-PORTO), Porto, Portugal
[3]Faculty of Medicine, University of Porto, Porto, Portugal
[4]Unit of Study and Treatment of Pain, Instituto Português de Oncologia do Porto Francisco Gentil (IPO-PORTO), Porto, Portugal
[5]Biomedical Research Center, Faculty of Health Sciences, Fernando Pessoa University, Porto, Portugal
[6]Research Department, Portuguese League Against Cancer, Porto, Portugal

Financiamento e conflitos de interesse:
This work was developed as part of a project selected as an internal clinical research project of Francisco Gentil Portuguese Institute of Oncology, Porto, Portugal (Bulletin 8/2017, CI -IPOP 70/2017). CV reports personal fees from F. Hoffmann-La Roche Ltd and Grünenthal, S.A., outside the submitted work. All the other authors have declared no conflicts of interest.

Autor para corrêspondencia:
Cláudia Vieira, Medical Oncology Department, Instituto Português de Oncologia do Porto Francisco Gentil (IPO-PORTO),
Rua Dr. António Bernardino de Almeida, 4200-072 Porto – Portugal.
Email: claudiampvieira@gmail.com;
Phone: 351 22 508 40 00 (ext. 7627);
Fax: 351 22 508 40 01.

Resumo

Objetivos: A dor é um problema frequente em Oncologia. No entanto, estudos retrospectivos sobre este tema geralmente apresentam diversos problemas, para avaliar e quantificar corretamente a dor, nomeadamente pela falta de registos de dor. Realizamos um estudo observacional para responder à questão: Os registos de dor coincidem entre profissionais de saúde (enfermeiros e médicos) e como é que esse fato afeta o resultado clínico?

Métodos: Estudo retrospectivo de uma única instituição com pacientes adultos. Internado em unidade de atendimento médico de 1º de fevereiro a 28 de fevereiro de 2007. Dados de dados demográficos do paciente e avaliação e tratamento da dor por enfermeiras e médicos foram coletados de prontuários clínicos.

Resultados: No geral, 140 internações de pacientes foram incluídas em nossa amostra: 74% dos os pacientes eram do sexo masculino; a idade média no diagnóstico foi de 59 anos (17-81 anos) e o diagnóstico mais frequente foi câncer gastrointestinal (38%). Registros de enfermeiras de a dor do paciente apresentou 13 (9,3%) internações com dor e 75,7% não tinham registro de queixas de dor. Os médicos relataram que a dor foi identificada em apenas 11 (7,9%) dos todas as admissões (46,4% sem registro de dor).

Características correspondentes de dor foram encontradas em 58 internações (41,4%). A sobrevivência era relacionado ao tipo de admissão: em geral, a narrativa da dor relatada pelo médico foi associada com pior sobrevida apenas no subgrupo de cânceres não gastrointestinais (p = 0,028). Dor relatada por pacientes a médicos em admissões programadas para quimioterapia foi associada a pior sobrevida (p = 0,018).

Conclusões: Nenhuma avaliação de correspondência entre os profissionais de saúde é reconhecida dificuldade como é sugerido por este estudo. Quando os médicos totalmente caracterizam a dor, eles podem identificar um subgrupo de pacientes com menos chance de sobreviver.

Palavras-chave: Dor, Profissionais de saude, Avaliacao, Cancro, Registo, Sobrevivencia, Enfermeiros, Medicos.

Abstract

Objectives: *Pain is a frequent issue in cancer patients; however, papers on this matter usually acknowledge a number of difficulties in evaluating and correctly controlling that pain, starting with a pain record. We undertook an observational study to answer the question: Do pain narratives match between health professionals (nurses and physicians) and how does this impact on the clinical outcome?*

Methods: *This was a single institution, retrospective study, with adult patients admitted to a medical care unit from 1 February to 28 February 2007. Data on patient demographics and pain evaluation and treatment by nurses and physicians were collected from clinical files.*

Results: *Overall, 140 patient admissions were included in our sample: 74% of the patients were male; the median age at diagnosis was 59 years (17–81 years) and the most frequent diagnosis was gastrointestinal cancer (38%). Nurses' records of patient pain showed 13 (9.3%) admissions with pain and 75.7% had no record of pain complaints. Physicians reported that pain was identified in only 11 (7.9%) of all admissions (46.4% lacked any record of pain).*

Matching pain characteristics were found in 58 admissions (41.4%). Survival was related to the type of admission: overall, physician-reported pain narrative was associated with worse survival only in the subgroup of non-gastrointestinal cancers ($p = 0.028$). Pain reported by patients to physicians in scheduled admissions for chemotherapy was associated with worse survival ($p = 0.018$).

Conclusions: *None matching evaluation among health professionals is a recognised difficulty as is suggested by this study. When physicians full characterises pain, they can identify a subgroup of patients with less chance to survive.*

Keywords: *Pain, Health professionals, Assessment, Cancer, Narratives, Survival, Nurses, Physicians*

Introduction

The assessment of long-lasting pain and the effects of treatment are more challenging than acute pain – both in patients suffering pain from non-malignant causes and in patients with cancer pain.[1-3]

Unrelieved cancer pain has an adverse impact on quality of life. While routine screening and assessment forms the basis of effective cancer pain management, it is often poorly done; thus it contributes to the burden of unrelieved cancer pain.[4] When treating the worst pain reported by the patient, the goal is to reduce symptom severity and to increase function, allowing for a better performance status and better performance of activities of daily living. Together, these will lead to better overall quality of life.[5,6]

Effective pain management is both a national and a global challenge. Lack of integration of current knowledge and practice of effective pain management by health professionals (HPs) in day-to-day care adversely affects patients and may result in unnecessary physical, psychological and emotional manifestations. Lack of proficient and uniform pain assessment is one of the most challenging barriers in achieving adequate pain control for patients.[7] Pain assessment is only the first step in effective pain management, but the consequence of that information can make a marked difference for a patient.[8] In clinical practice, the assessment of location and intensity of pain is usually considered to be sufficient.[1] Pain descriptors and intensity are the two most frequent features reported as shown in the literature related to this topic. However, these pain characteristics are insufficient for the majority of pain syndromes. Therefore, an incomplete pain evaluation without a correct record of its characteristics may lead to a high probability of unsuccessful treatment.[9] The emergence of new drugs for neuropathic pain, or the neuropathic component of mixed pain or the breakthrough cancer pain, reinforces the need of a more comprehensive approach.[10] In turn, this may lead to a more accurate prescription according to the pain mechanism as an important part of the process.

If HPs have inadequate information or knowledge regarding cancer pain, they will not be able to provide good quality patient care.[11-13] The most acknowledged and recognised barrier to effective pain assessment is subjectivity of the individual and their personal and private experiences within the dimensions of pain management.[14] Assessment of pain requires that HPs become well educated in recognising an individual patient's perception of pain, their previous experiences with pain, their current knowledge of pain, their spiritual and religious beliefs, and any sociocultural components.[15]

Because pain is such a subjective, personal and private experience, assessing pain in patients that cannot communicate well is difficult – particularly in patients suffering cognitive impairment and dementia.[1]

In a systematic review of institutional interventions designed to improve the assessment and treatment of pain in hospitalised cancer patients – to assist cancer centres with improving their pain management – Goldberg et al.[7] identified five interventions with particular relevance in pain management: (1) professional and patient education; (2) regular pain assessment (pain as a vital sign); (3) audit of pain results (and feedback to clinical staff); (4) digital decisional support systems; and (5) specialist-level pain units. However, data from that review were generated from small observational studies. Moreover, in these studies, success was described as (1) an increase in the patient satisfaction index; (2) an increase in the pain intensity documentation; and (3) an improvement in the knowledge of nurses. None of these studies compared physicians and nurses records or reported successful interventions in improving pain severity or patient survival.[16] Recent similar studies with particular focus on hospitalised children, evaluated the quantity, quality and structure of the pain records; the conclusion consistently led to the need of improvement beyond the visual or the numeric scale.[17,18] With regard to nurses recording adult pain, reports indicate a suboptimal documentation of pain management (even in cancer centres).[19,20]

Numerous instruments have been developed for different subtypes of chronic pain in order to assess qualitative aspects of pain and its impact on patient function.[21,22] The long list of published instruments indicates that pain assessment continues to be a challenge.[3] Although patient satisfaction with pain management has significantly improved since the adoption of pain management standards, it is important to notice that adverse drug reactions have more than doubled. For the treatment of pain to be safe and effective, we must consider more than just a one-dimensional numerical assessment of

pain.[2] Valid and reliable assessment of pain is essential for both clinical trials and effective pain management.[3]

In Portugal, pain must be recorded as the fifth vital sign, in accordance with a National Health System (NHS) directive that was set in 2003. In order to test the quality of pain records, the authors undertook an observational study aiming to answer the question: Is cancer pain systematically and homogeneously evaluated in hospitalised cancer patients in a cancer centre? Do pain narratives match between health professionals (nurses and physicians) and how does this impact on the clinical outcome?

Methods

Participants and procedures

We undertook a retrospective study in a single cancer centre, including adult inpatients (patients) admitted to a medical oncology department (the section of gastrointestinal, lung, head and neck, bone and soft tissue cancers), between 1 February and 28 February 2007. A total of 140 admissions were evaluated from 119 patients (no admitted patient was excluded). Local and National Ethics Committee considerations and the Helsinki Declaration guidelines were respected.

Data collection procedures

The 140 admissions were included in our sample during the stated 1-month period; however, epidemiologic and survival analyses included 119 patients at their first admission (2 patients were admitted more than once). Twenty-one patients were admitted more than once (4 patients had three admissions).

Measures

Data were collected from clinical files regarding patient characteristics (age, gender, race, education, urban or rural address, cancer type, cancer diagnosis date, actual disease status, intent of treatment, date of last observation or death); date of admission, reason for being admitted as an inpatient (and whether it was a scheduled or emergency hospitalisation); and discharge date of each hospitalisation.

Pain evaluation (all pain narratives during that hospitalisation) by the nurses and the physicians were also collected from clinical files. Data from pain narratives were explored from both a quantitative and a qualitative point of view. The presence or absence of some reference to pain in the HPs' narratives and matching registries were evaluated. A quantitative analysis of pain prevalence was performed if the HP described the patient's pain, and quantitative and qualitative analyses of the pain description were also executed (pain characteristics were: location, intensity, quality, radiation, releasing/aggravating factors, analgesic/rescue response). Survival date was actualised in 2017, to determine the impact of systematically and homogeneously evaluation of cancer pain on the clinical outcome.

Analyses

Data on quantitative and qualitative pain narratives in the clinical files of physicians and nurses were analysed. Descriptive analyses were used to examine the demographic and pain data in this study. Statistical analysis used SPSS software (version 17.0; SPSS, Inc., Chicago, IL); the Chi-square test and the log-rank test were applied; $p < 0.05$ was considered statistically significant. Overall survival was defined as the time elapsed from diagnosis to the last observation or death. Deaths were considered events. Survival curves were determined by the Kaplan–Meier method.

Results

Description of participants

In our studied population (119 patients), the male Caucasian patients were the majority (71.4%) with a median age at diagnosis of 59 years (range 17–81 years; Table 1). The most frequent cancers were gastrointestinal (represented by 38% of patients) and lung (24%) followed by head and neck (19%).

The majority of patient admissions (88.6%) were for scheduled chemotherapy (59 with curative and 65 with palliative intent) and the remaining admissions were for best supportive care or adverse event treatment.

Pain evaluation and narratives

In Tables 2 and 3, data concerning the 140 patient admissions are presented. Nurses' recorded pain in 13 (9.3%) patients, and physicians recorded 11 (7.9%) patients with pain. A significant association ($p < 0.001$) was found between physicians and nurses in relation to the presence of any kind of reference to pain in the clinical file (Table 2).

Nurses' patient records denied the presence of pain in 75.7% of cases, and made no reference to the presence or absence of pain in 15%. In comparison, physicians' patient records made no reference to pain in 46.4%.

Of the 13 patients with pain noted by nurses, pain location and/or some pain characteristics were noted in 8 (pain radiation [1 patient], quality [n = 2], aggravating factors [n = 2]); response to analgesic therapy in 4; rescue medication in 5; and intensity in 8.

Of the 11 patients with pain noted by physicians, location was described in 10 and some pain characteristics in 3 (pain radiation [2 patients], and aggravating factors [n = 4]); response to analgesic therapy in 2; rescue medication in 1; and intensity in 3 (Table 2).

The narratives were coincident in 58 admissions (41.4%): 4 reported the presence of pain and 54 the absence of pain. In 12 cases (8.6%), no narrative of pain either by physicians or nurses was observed (Table 3). The records of nurses and physicians matched for pain characterisation in 1 case and for location in 2 (Table 2). A significant association ($p = 0.009$) was

Table 1. Sociodemographic characteristics of 119 patients.			
Variable		N	%
Gender	Male	85	71.4
	Female	34	28.6
Age	< 20	2	1.7
	20–29	4	3.4
	30–39	8	6.7
	40–49	25	21
	50–59	21	17.7
	60–69	40	33.6
	70–79	18	15.1
	80–89	1	0.8
Totals		119	100

Table 2. Frequency of pain registry and characteristics of pain by subgroup of health professionals (n = 140).				
		Health professional		p
		Physicians	Nurses	
Pain narratives	No registration	65 (46.4%)	21 (15%)	**<0.001**
	With registration	75 (53.6%)	119 (85%)	
Pain prevalence	Pain presence	11 (7.9%)	13 (9.3%)	>0.05
	Pain absence	64 (45.7%)	106 (75.7%)	
Pain characteristics		*(N= 11)*	*(N = 13)*	*Not applicable*
	Location	10	8	
	Intensity	3	8	
	Quality	0	2	
	Radiation	2	1	
	Releasing/ aggravating factors	4	2	
	Analgesic/ rescue response	2/1	4/5	

found between the matching characteristics of the pain narratives of the nurses versus the physicians (Table 3). No relation was found between pain records and primary tumour location or reason for admission, for either physicians' or nurses' patient records.

Survival analysis

Survival analysis was performed based on data collected in 2017 and included 119 patients from their first admission during the study period (1 February to 28 February 2007): 11 patients were alive in follow-up, and the median overall survival was 22 months. Females had a better median overall survival (31 months) compared with men (21 months), with statistical significance (p = 0.026). There was no gender difference on pain in the HP narratives, and the three groups (pain presence, pain absence and lack of registration) were well balanced between the two genders. Regarding the existence (or not) of some reference to pain in the daily narratives from the HPs, no association with survival was found.

When the analysis was between two groups – pain presence or pain absence – the presence of pain (report by physicians) showed a trend toward worst survival, although this did not reach statistical significance (p = 0.062). However, the presence of physician pain narratives was associated with worse survival in the subgroup of non-gastrointestinal cancers (p = 0.028). No difference was found in the patient pain records reported by nurses.

Table 3. Cross table of pain registry by subgroup of health professional and matching narratives (n = 140).

		Physicians			Total	p
		With pain	Without pain	No registry		
Nurses	With pain	4	3	6	13 (9.3%)	
	Without pain	5	54	47	106 (75.7%)	0.009
	No registry	2	7	12	21 (15%)	
Totals		11 (7.9%)	64 (45.7%)	65 (46.4%)	140 (100%)	

Table 4. Pain registry by subgroup of health professional and association with overall survival (n = 119).

Association with overall survival	Physicians p*	Nurses p*
Pain registration	0.118	0.822
Pain presence	0.062	0.730
Pain presence in non-GI cancers	**0.028**	0.581
Pain presence by gender	0.077 *(male)*	0.061 *(female)*
Pain presence by type of admission	**0.018** *(scheduled chemotherapy)*	0.793 *(scheduled chemotherapy)*
Location of the pain	**0.042**	0.616

*(log rank test)
GI – gastrointestinal.

When these data were analysed by gender, a trend was identified: males with pain had worse survival; however, this did not reach statistical significance (p = 0.077). Physician reporting the presence of pain in a scheduled admission to chemotherapy was associated with worse survival (p = 0.018).

In comparison, nurses' reporting the presence of patient pain in a scheduled admission was not associated with survival (p = 0.793). However, when these data were analysed by gender a trend was identified: females with pain had worse survival; however, this did not reach statistical significance (p = 0.061).

Survival was worst when the location of the pain was described by physicians (p = 0.042); however, this was not the case when nurses reported the pain location.

Discussion

To the best of our knowledge, our study is the first to explore the matching of pain records between two groups of HPs. Some published studies refer to the descriptive nature of the majority of pain records or the existence of scarce records generated by the application of unidimensional scales. Particularly in the paediatric setting and acute pain, there are many proposed charts that help to full pain characterisation. However, the usefulness of these charts in clinical practice and the daily routine are not consistent.

Although pain has been considered the fifth vital sign since 2003 and is included as part of routine patient evaluation, the records from different health professionals are often inaccurate and contradictory. Our retrospective study included 119 inpatients of the Medical Oncology Department, relating to 140 admissions for 4 consecutive weeks. Almost half of these admissions (46%) had no pain reported in their medical records. As for the characteristics of pain, the intensity was reported in only 3 cases by the medical staff (2%) and 8 cases by the nursing staff (5.7% of the total). Since the number of inpatients on chemotherapy represented 88.5% of the group, it is possible that the low prevalence of pain may have been biased by the current use of steroids as antiemetics for almost all patients admitted for scheduled chemotherapy. However, for patients on palliative chemotherapy, if we consider that quality of life is a main objective, it may be that 58% of the inpatients are in jeopardy for uncontrolled pain. These observed results may be related to underevaluation and underreporting of pain, because the onset of chronic pain may be a consequence of undertreatment of the acute pain of invasive procedures or other adverse events.

Among HPs, nurses seem to record patient pain much more often than physicians. We must consider that, in their daily role, nurses usually check vital signs of patients three times a day, and their chance of missing a parameter is minimal. However, we must point out that the percentage of non-recording is still high (15% for nurses, 46.4% for physicians) considering the fact that pain evaluation is mandatory according to the NHS guidelines. The same reasoning may apply for the response of pain either to basal analgesia or to rescue medication. As a consequence of the non-recording of pain, drug titration during patient monitoring, if needed, will happen over longer

periods with an increased risk of adverse events and worse overall results.

Improved survival was observed in females compared with males. This gender difference was not explained by the occurrence of more pain reports in female patients. However, cancer prevalence may explain this fact, taking into account the type of tumours present in this group of patients. When we considered a subgroup of tumours presenting worse prognosis (lung, head and neck, bone, soft tissues), the record of pain was relevant to survival evaluation – but only if the pain had been reported by physicians or if they referrer pain location in their reports. However, no relation was found between survival and the nurses' reports. Pain reports by physicians in scheduled hospital admissions had a significant impact on survival. In the nurses' pain reports, this relation was not found; however, the missing data may represent a bias.

Currently in hospital logistics, the sharing of functions by nurses and other HPs, which were traditionally attributed to physicians, is increasing. In developed countries, patient overall survival is increasing and resulting in a higher clinical burden of care, making it necessary to share data collection and patient (and caregivers) teaching functions with nurses. However, this work compels us to reflect not only on the need for serial pain assessments (with better description and appropriate tools), but also whether the physician is better trained to recognise a serious situation. When physician records described the presence of pain and some characteristics such as location, survival was worse. Pain evaluation by the physician seems relevant to survival. This is particularly true in patients scheduled to undergo chemotherapy (requiring prolonged infusion of drugs over several days and hydration regimens such as cisplatin).

Good pain records by physicians can have an economic impact, improving palliative care and avoiding unnecessary tests and treatments, which is also important to the national health systems. It is recognised that a good physician–patient relationship improves clinical outcomes and satisfaction rates, and decreases the demand of diagnostic and laboratory tests, prescriptions, hospitalisations and other healthcare consulting. Patient-centred care is determined by what matters to the patient.[2,5] This study adds information that reinforces the message that pain characterised by physicians matters for better pain control. Interviews with physicians seem more accurate to identify cases with severe pain and may influence patient survival.

The mismatch of pain records between HPs and real pain prevalence has been reported in other studies. Non-coincident data among HP evaluations is a recognised difficulty in various studies and was suggested by this work.

One limitation of this study is that data relate to only 1 month of hospitalisation and only a small number of patients had pain. This small sample size may weaken our findings. Despite the progress made since 2007 (institutions have likely made pain assessment a priority), we believe that this study still represents a very necessary and current warning for HPs. The biggest limitation of this study is its old age and the fact that there is now greater awareness of the problem of consistent recording of patient pain. However, there is still a long way to go in terms of systematic pain assessment and its subsequent correct treatment. Moderate to severe pain almost always requires the use of opioids, judiciously, but without exaggerated phobias or unfounded beliefs.

The future direction for this research is the implementation of computer tools that allow this type of study to be carried out on a larger scale and with several time evaluations in order to consolidate the results obtained. Another aspect is the application of questionnaires for pain and quality of life from patients with chronic cancer pain. This is possible and desirable during clinical practice, in day-to-day patient interviews and in clinical trials. Its application on a regular basis will allow a more accurate comparison between subgroups, which will result in higher quality literature and appropriate national guidelines to more successfully control cancer pain.

Effective pain management is both a national and global challenge; as such, the final message is to regularly screen all patients for pain and to perform a comprehensive pain assessment when pain is present. If pain exists in reality but is not reported in the patient's records then it does not exist. If it does not exist, it will not be treated. If it is not treated, the goal of 80% pain control will not be achieved. In turn, if we do not achieve proper pain treatment, a national policy will remain elusive, which may be a legal issue in the near future.

Conclusions

Cancer pain is a factor that has the greatest impact on quality of life. For proper cancer pain control, HPs should comply with standards of care established by the World Health Organization or other guidelines of pain management.

Lack of integration of current knowledge and the practice of effective pain management by HPs into day-to-day care adversely affects patients and results in unnecessary physical, psychological and emotional manifestations.

A lack of proficient and uniform pain assessment is one of the most challenging barriers in achieving adequate pain control. This study reminds us that physicians cannot abstain from the assessment of pain and its correct characterisation as this may impact patient survival.

Acknowledgements

'Pain in Hospitalised Oncology Patients: Nurses' and Physicians' Records' has been presented has a poster at EFIC – Pain in Europe VI Congress, from 9 September to 12 September 2009 in Lisbon, Portugal.

Medical Oncology and Hematology Department (Alexandra Teixeira, Marta Juan), Unit of Study and Treatment of Pain and Nursing Staff (Jorge Freitas) of Francisco Gentil Portuguese Institute of Oncology, Porto, Portugal.

References

1. Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. Br J Anaesth. 2008;101(1):17-24.
2. Sequeira MI, Sousa N, Fragoso M, Silva A, Pereira F, Azevedo L. Single centre prospective study of systematic pain evaluation in Portuguese patients with metastatic prostate cancer. Acta Medica Portuguesa. 2017;30(11):796-804.
3. Bassols A, Bosch F, Campillo M, Canellas M, Banos JE. An epidemiological comparison of pain complaints in the general population of Catalonia (Spain). Pain. 1999;83(1): 9-16.
4. Phillips JL, Heneka N, Hickman L, Lam L, Shaw T. Can A Complex online intervention improve cancer nurses' pain screening and assessment practices? Results from a multicenter, pre-post test pilot study. Pain Manag Nurs. 2017;18(2):75-89.
5. Hadi S, Fan G, Hird AE, Kirou-Mauro A, Filipczak LA, Chow E. Symptom clusters in patients with cancer with metastatic bone pain. J Palliat Med. 2008;11(4):591-600.
6. Angel S, Jensen LD, Maribo T, Gonge BK, Buus N. Narratives of life with long-term low back pain: A follow up interview study. Scand J Pain. 2017;17:382-389.
7. Patient Safety and Quality: An Evidence-Based Handbook for Nurses Ronda G Hughes , editors. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 Apr. Advances in Patient Safety. PMID: 21328752 NBK2651 Free Books & Documents
8. Merina V. Improving patients' pain management through proper documentation. The University of San Francisco Scholarship; Geschke Center. Master's Projects and Capstones. 2016: 298.
9. Vieira C, Fragoso M, Pereira D and Medeiros R. Pain prevalence and treatment in patients with metastatic bone disease. Oncology Letters 2019;17:3362-3370.
10. Ferreira Pereira F, Azevedo S, Magalhaes H, Vieira C, Pereira D and Fragoso M. Three case reports of chronic pain with neuropathic component - the importance of individualized therapy. EJMCR. 2018;2(3):91-94.
11. Skorpen F, Laugsand EA, Klepstad P, Kaasa S. Variable response to opioid treatment: any genetic predictors within sight? Palliat Med. 2008;22(4):310-327.
12. Oliveira A, Dinis-Oliveira RJ, Nogueira A, et al. Interleukin--1beta genotype and circulating levels in cancer patients: metastatic status and pain perception. Clin Biochem. 2014;47(13-14):1209-1213.
13. Oliveira A, Dinis-Oliveira RJ, Nogueira A, et al. Genetic profile and cancer-related pain: a tale from two outlier cases with bone metastatic disease. Pain Med. 2014;15(4):710-712.
14. Greenwald HP. Interethnic differences in pain perception. Pain. 1991;44(2):157-163.
15. Glowacki D. Effective pain management and improvements in patients' outcomes and satisfaction. Crit Care Nurse. 2015;35(3):33-41.
16. Goldberg GR, Morrison RS. Pain management in hospitalized cancer patients: a systematic review. J Clin Oncol. 2007;25(13):1792-1801.
17. Rashotte J, Harrison D, Coburn G, Yamada J, Stevens BJ, Pain CIHR Team in Children's Pain. Health care professionals' pain narratives in hospitalized children's medical records. Part 2: structure and content. Pain Res Manag. 2013;18(5):e84-93.
18. Rashotte J, Coburn G, Harrison D, et al. Health care professionals' pain narratives in hospitalized children's medical records. Part 1: pain descriptors. Pain Res Manag. 2013;18(5):e75-83.
19. Adams JA, Bailey DE Jr., Anderson RA, Docherty SL. Nursing roles and strategies in end-of-life decision making in acute care: a systematic review of the literature. Nurs Res Pract. 2011;2011:527834.
20. Song W, Eaton LH, Gordon DB, Hoyle C, Doorenbos AZ. Evaluation of evidence-based nursing pain management practice. Pain Manag Nurs. 2015;16(4):456-463.
21. Vieira C, Brás M and Fragoso M. Opióides na Dor Oncológica e o seu Uso em Circunstâncias Particulares: Uma Revisão Narrativa Opioids for Cancer Pain and its Use under ParticularbConditions: A Narrative Review. Acta Med Port 2019;32(5):388-399.
22. Pereira Vieira CM, Fragoso M, Ferreira M, Ferreira Pereira F, Pereira D and Medeiros R. The history of cancer pain and bone-targeted agents: 10 most commonly asked questions. Cancer Manag Res. 2018;11:37-46.

Caso clínico

Tumor filóide da mama recidivante: caso clínico

Phyllodes breast tumour with repeated recurrences: case-report

Autor:
Natacha Abreu[1*], Juliana Filipe[2], Saudade André[3], João V. Moniz[4], José C. Marques[5]

Afiliação:
[1] Resident in Radiology, Radiology Department, Funchal Central Hospital, SESARAM E.P.E. [2] Resident in Pathology, Pathology Department, Portuguese Institute of Oncology of Lisbon (IPOLFG). [3] Breast Pathologist, Pathology Department, Portuguese Institute of Oncology of Lisbon (IPOLFG). [4] Breast Surgeon, Surgery Department and Breast Clinic, Portuguese Institute of Oncology of Lisbon (IPOLFG). [5] Senior Consultant in Breast Radiology, Radiology Department, Portuguese Institute of Oncology of Lisbon (IPOLFG).

Financiamento:
No funding was attributed to the conception/preparation of the present article. The authors declare no conflict of interest.

Autor para correspondência:
Natacha Nóbrega de Abreu
Address: Rua Manuel Marques, nº 2, 4D, 1750-171 Lisboa, Portugal
Email: natachanobregaabreu@gmail.com

Resumo

O tumor filóide é um tumor fibro-epitelial que corresponde a 0.3-1% de todos os tumores primários da mama e inclui as categorias benigno, *borderline* e maligno. A maioria tem um comportamento benigno, com uma taxa de recidiva local estimada em 21%. Apresentamos o caso de uma mulher de 58 anos, com um tumor de 20 cm na mama esquerda, submetida a mastectomia simples em 2011, com o diagnóstico de tumor filóide *borderline*. Desde então apresentou cinco recidivas locais. Os factores preditivos de recidiva local são as margens cirúrgicas e determinados parâmetros histológicos. Não existem sinais imagiológicos consistentes que permitam prever o risco de recidiva, nem diferenciar definitivamen te entre tumor filóide/fibroadenoma nem entre as categorias histológicas do tumor filóide. Acresce a heterogeneidade estrutural intrínseca destes tumores que dificulta o diagnóstico definitivo em biópsia. Neste artigo, sublinhamos a importância da correlação clínica, radiológica e anatomo-patológica para a correcta abordagem destes tumores. Aditionally, internal cell distribution/representation is not homogeneous, which may a representative biopsy and preclude the diagnosis.

Palavras-chave: Tumor filóide, Mama, Fibroadenoma, Ressonância magnética, Ecografia.

Abstract

A phyllodes tumour is a fibro-epithelial tumour accounting for 0.3%–1% of all primary breast tumours and is pathologically diagnosed as benign, borderline and malignant. Most behave benignly, with local recurrences occurring at an overall rate of 21%. We report the case of a 58-year-old woman who presented a 20 cm tumour in the left breast, which was treated with a simple mastectomy and diagnosed as a borderline phyllodes tumour. She then had five local recurrences. Predictive factors for local recurrences are the status of surgical margins and some histological parameters. No reliable imaging features can predict the risk of local recurrence, or enable differentiation between a phyllodes tumour and a fibroadenoma, or between histological categories of a phyllodes tumour. Also, the intrinsic structural heterogeneity of these tumours difficult the definitive diagnosis in biopsy. We emphasise the need for clinical, radiological and pathological correlation in order to attain the best approach for these tumours.

Keywords: *Phyllodes tumour, Breast, Fibroadenoma, Magnetic resonance, Ultrasound.*

Introduction

Phyllodes tumours (PTs) of the breast are fibroepithelial neoplasms, which histologically resemble an intracanalicular fibroadenoma but with hypercellular stroma. They are characterised by a myoepithelial and epithelial component arranged in clefts surrounded by a hypercellular stroma/mesenchymal component, resembling a leaf architecture. The tumour name is derived from the Greek *'phullon',* meaning 'leaf' (**Fig. 1**).

PTs account for less than 1% of all breast tumours and approximately 2%–3% of all fibroepithelial lesions. They occur predominantly in middle-aged women (average age at presentation, 40–50 years), about 15–20 years later than fibroadenomas.[1] They often present as a rapidly growing firm or hard nodule with an average size of 4–5 cm. A PT may present a morphologic continuum from benign to malignant. The World Health Organization (WHO) proposed a classification of three categories (benign (60%–75%), borderline (13%–26%) and malignant (10%–20%), based on a semi-quantitative assessment of stromal cellularity, cellular pleomorphism, mitotic activity, tumour margin/border appearance and stromal overgrowth.[2] The structural heterogeneity may lead to non-representative tissue sampling in biopsy, as the histological features characteristic of high-grade tumours may be focal. This explains core needle biopsy false negatives being reported as high as 30%,[3] and the need for excision to accurately classify and grade PT. Some imaging features favour phyllodes instead of fibroadenoma (e.g. the presence of internal cystic areas). However, no imaging characteristics can predict the risk of recurrence, which have been reported in 10%–17% for benign PTs, 14%–25% for borderline PTs and 23%–30% for malignant PTs;[2] neither can they differentiate between benign, borderline and malignant phyllodes. Thus, the role of imaging is to identify the early signs of recurrence. In this case report, we describe imaging and pathological features of a peculiar case of a recurrent borderline PT with loss of epithelial components in the recurrences.

Case report

A 58-year-old woman presented to the Department of Breast Diseases of The Portuguese Institute of Oncology of Lisbon in April 2011 with a huge tumour (approximately 20 cm) on the left breast. The tumour was hard on palpation, without ulceration or remarkable skin-colour changes. There were no associated enlarged axillary lymph nodes. Magnetic resonance (MR) (**Fig. 2**) exhibited a large relatively well-circumscribed mass, markedly heterogeneous, with irregularly shaped cystic and solid components. The solid component showed marked restriction on diffusion-weighted imaging (DWI) and corresponding low apparent diffusion coefficient (ADC) values (**Fig. 3**). Overall, these imaging findings were highly suggestive of malignancy.

A core needle biopsy entailed a diagnosis of PT with probably benign characteristics. However, the surgical specimen's histology fulfilled the WHO criteria for a borderline PT, which was different to the imaging findings.

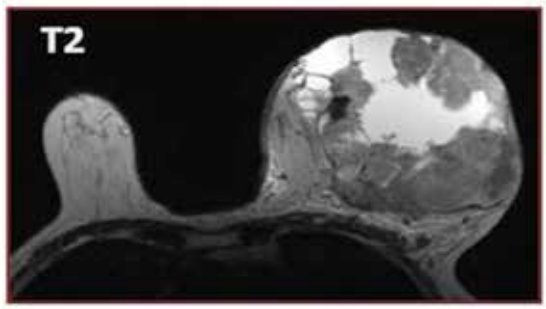


Figure 2. Magnetic resonance (MR) of a 58-year-old woman with a hard 20 cm borderline phyllodes tumour of the left breast. Note the irregular shaped cystic spaces and the heterogeneous intermediate-to--low signal solid component in T2, also irregularly shaped. No enlarged axillary lymph nodes were noted. The subtracted post-gadolinium images in the early and delayed phases (not exhibited) show that the solid component enhances slowly and heterogeneously, and plateaus in the delayed phase, profiling a type 2 kinetic curve.

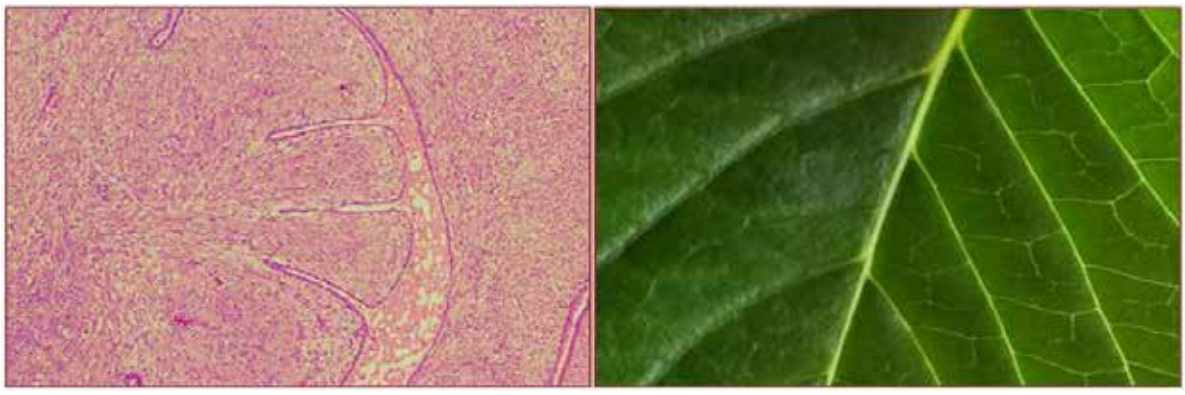


Figure 1. Phyllodes tumour with intracanalicular growth pattern with leaf-like projections capped by epithelium protruding into dilated elongated lumina, resembling a leaf structure.

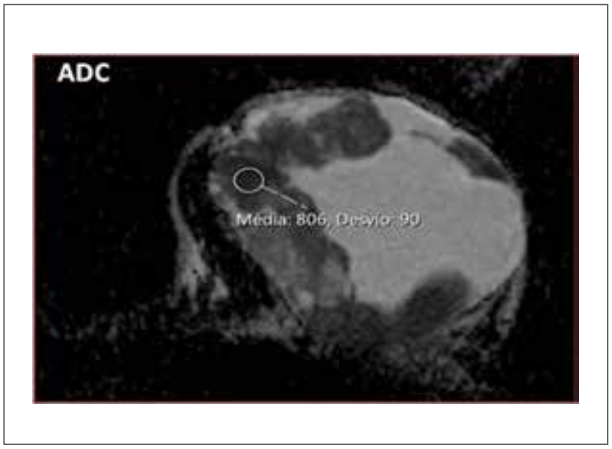


Figure 3. Same magnetic resonance as depicted in Fig. 2. In diffusion-weighted imaging (DWI), the solid component shows marked restriction especially in the most anterior section (b 1000). Apparent diffusion coefficient (ADC) values are low, with a mean of 806. These findings are highly suggestive of malignancy, which differed from the pathology diagnosis.

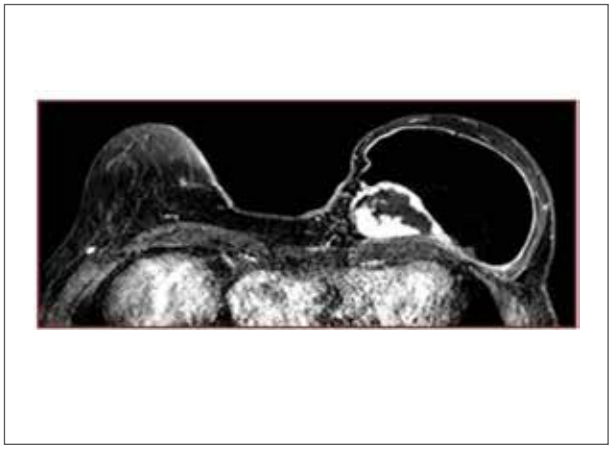


Figure 4. Magnetic resonance, late (5 minutes) post-gadolinium administration. Five years after the first diagnosis of a borderline PT, a new nodule was noticed in the reconstructed left breast, posterior and medial to the prosthesis. The lesion had a cystic and a solid component, which showed a heterogeneous signal in T2 and homogeneous isointensity in T1 FS (both not shown). After gadolinium administration, the solid component showed early marked and persistent enhancement.

p = phyllodes tumour.

The patient underwent a simple skin-sparing mastectomy of the left breast followed by reconstruction with a prosthesis and a latissimus dorsi flap. The tumour was adjacent to the pectoral fascia, while the remaining surgical margins were equal or superior to 10 mm.

Approximately 5 years later, in January 2016, a subcutaneous nodule was detected in the same patient, which was excised and diagnosed as a recurrent PT, without an epithelial component. In MR imaging (pursued in March 2016; **Fig. 4**) it corresponded to a complex cystic and solid circumscribed mass of about 7 cm. It was adjacent to the posterior surface of the prosthesis and was pushing it.

A recurrence of PT was assumed and the patient underwent a wide lumpectomy, which included the prosthesis and the pectoralis major muscle, with a distance of 1 mm from the closest surgical free margin (inferior). Pathology confirmed a recurrence of PT, with moderately cellular stroma, exhibiting two mitosis/10 high-powered field (HPF, 400×). No epithelial or heterologous components were seen.

Five months later (August 2016) this patient noticed a new nodule of about 3.6 cm in the left axillary tail (a different site from the previous one). A lumpectomy was performed and the histopathology was consistent with recurrent PT, with no epithelial component. This new lesion behaved differently: it had infiltrative borders, hypercellularity and 10 mitosis/10 HPF. Tumour margins were coincident with the surgical margins.

Nine months later (June 2017), a follow-up MR (**Fig. 5**) uncovered a small nodule in the left axillary tail. The patient was again submitted to lumpectomy and the pathologic diagnosis was consistent with recurrence, with an identical histological pattern to the previous recurrences. The tumour's posterior surgical margin was 2 mm.

Seven months later (January 2018) she presented with a new recurrence of PT in the left axillary tail (**Fig. 6**) and was once more submitted to lumpectomy, also with coincident tumour/surgical margins. The histological pattern was similar to the other recurrences, but with an increased number of mitotic figures (**Fig. 7**). At this point, radiotherapy was suggested, but the patient refused.

Figure 5. Magnetic resonance shows a well circumscribed nodule of 12 mm on the left reconstructed breast, anterior and lateral to the prosthesis, which corresponded to a second recurrence. The lesion exhibited an early pronounced and persistent enhancement, profiling a type 2 curve. The nodule showed restriction on DWI studies (b1000), but the corresponding ADC value was high (1.6).

ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging.

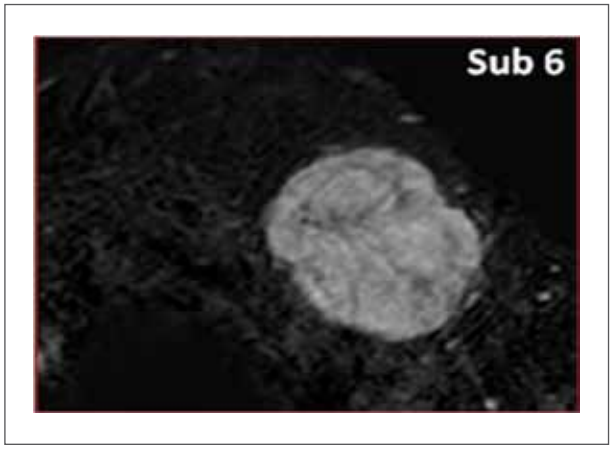


Figure 6. Magnetic resonance, subtraction post-gadolinium late image (Sub 6). The mass shows internal non-enhancing septations, which is a feature usually pointed as typical of fibroadenomas but also seen with phyllodes. The mass had well-defined margins, was entirely solid, and enhanced early and avidly with a steady kinetic (type 2 curve). The lesion exhibited marked restriction (b1000) with high ADC values (1.5).

ADC = apparent diffusion coefficient.

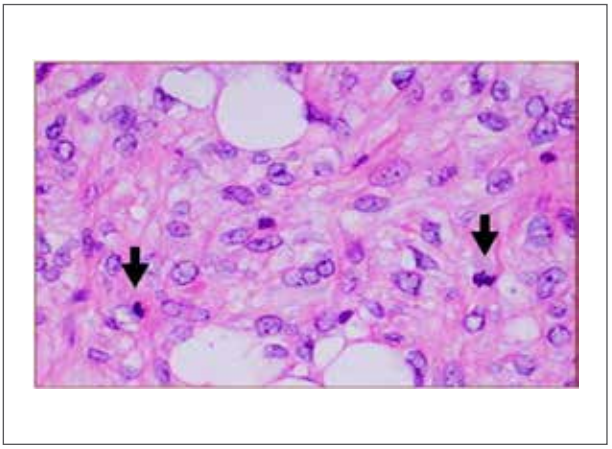


Figure 7. Corresponding histology of the same lesion depicted in Fig. 6. Phyllodes tumour recurrence with a histological pattern identical to that observed in the previous recurrences; however this lesion had an increased mitotic rate: 13 mitosis/10 HPFs (400×). No epithelial or heterologous components were seen. In this image, there are two mitotic figures (arrows) in one HPF.

HPF = high-powered field.

In December 2018, about 10 months after the last recurrence, she returned to the Department of Breast Diseases because of a new lump in the left upper outer quadrant. The ultrasound-guided biopsy confirmed a new recurrence. MR revealed a tumour consisting of multiple confluent nodules located in the left axillary tail of the left reconstructed breast. A lumpectomy of this 7 cm multinodular tumour was performed in February 2019. The closest margin was 1 mm. The histological pattern was identical to the previous recurrence.

The documentation of recurrences showed that no axillary or internal mammary adenopathies were documented.

This case is summarised in a time-event graphic (**Graphic 1**).

Discussion

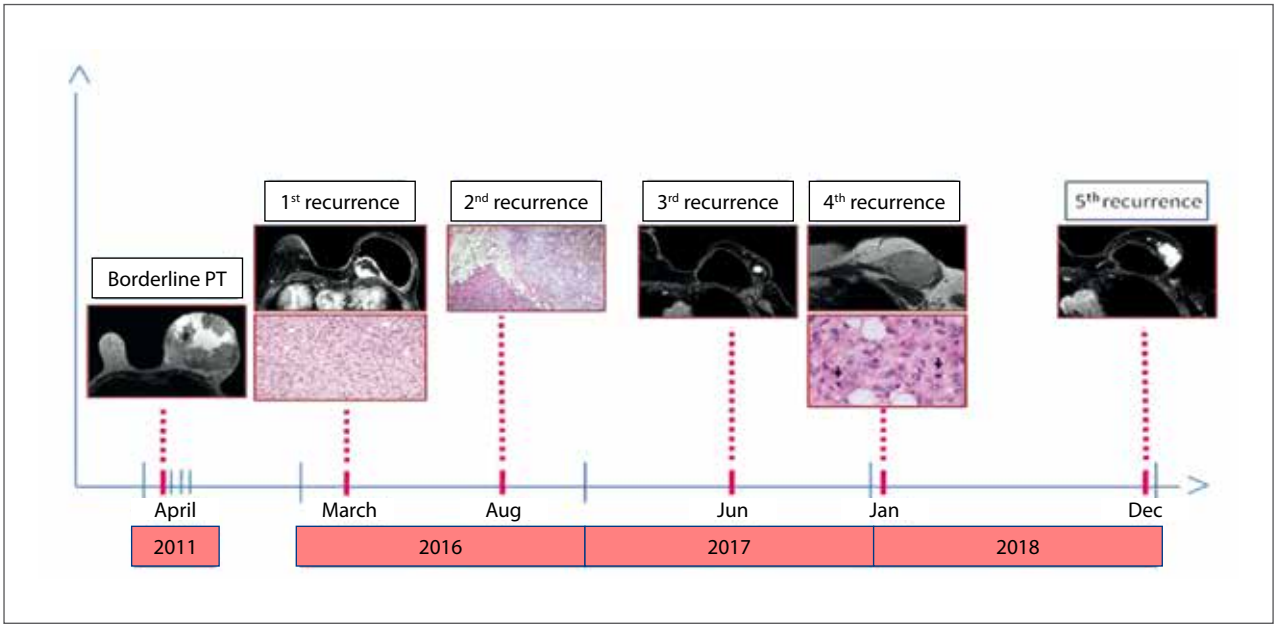
A PT is usually suspected in a peri-menopausal woman who presents with a well-circumscribed large nodular tumour (usually > 3 cm), with clinical rapid growth, and which looks similar to fibroadenoma on ultrasonography.

Some imaging features may favour a PT over a fibroadenoma, such as the presence of internal cystic spaces,[1] a round shape, lobulations and marked posterior enhancement (explained by the presence of intramural cysts representing areas of degeneration and focal necrosis).[1,4] Although the presence of internal non-enhancing septations have been classically described as being typical of fibroadenomas, they also have been documented in benign phyllodes (**Fig. 6**).

The role of imaging in distinguishing between the different subtypes of phyllodes is a strive. Tan et al.[5] suggested that irregular shape and larger size correlated with more likelihood of

Figure 8. Magnetic resonance of new lumps noted in the UOQ/axillary tail of the left reconstructed breast, anterior to the prosthesis, better appreciated in this MIP reconstruction. They show homogeneous T2 and T1 signal, isointense with the breast parenchyma, with no cystic areas. They enhanced early and steadily (type 2 curve). There was restriction in DWI (b1000) with high ADC values (2,0), which favoured a benign nature.

borderline or malignant phyllodes. Yabuuchi et al.[6] found that (i) cystic changes with an irregular wall, (ii) a tumour signal intensity higher than normal breast tissue signal intensity on T1-weighted images, and (iii) a tumour signal intensity lower than or equal to normal breast tissue signal intensity on T2-weighted images and/or low ADC on DWIs were indicative of malignant phyllodes of the breast. They suggested that low



Graphic 1.

ADC areas would match stromal proliferative areas and this could be used to map the most useful regions to biopsy, but there is a lack of consistency between the different studies. In this case, the initial tumour and the first recurrence had a cystic component, and all the remaining recurrences were entirely solid. It is interesting to note that despite a histological progression demonstrated by an increasing number of mitotic figures and cellularity, the imaging features did not resemble this – especially with regard to the enhancement pattern and the ADC values. In fact, the first pathological diagnosis on core needle biopsy suggested a benign tumour, but the surgical specimen provided the diagnosis of a borderline PT. Neither of these were concordant with the imaging findings, which revealed features highly suggestive of malignancy (**Fig. 3**). The structural intrinsic pathologic heterogeneity of these tumours, with features that may fall within a continuum, represents a real risk of non-representative tissue sampling on core biopsy; this was factual in our patient's first diagnosis on biopsy.

Local recurrences are known to occur with ranges of 10%–17%, 14%–25% and 23%–30% for benign, borderline and malignant PTs, respectively.[2] The status of surgical margins appears to be the most reliable predictive factor for recurrence.[2] The borderline tumour excised by mastectomy was adjacent to the pectoral fascia, while the other surgical margins were equal or inferior to 10 mm. There are some conflicting data in the literature regarding the recommended width of negative tumour margins. Although they are usually well defined, small tumour buds may protrude into the surrounding tissue. Such protrusive expansions are difficult to identify and may be left behind after surgical removal of the tumour, and are a source of local recurrence. Most authors recommend a minimum cut-off of 10 mm to reduce the risk of leaving some tissue behind that could allow a relapse, but recent data have shown that there is no direct relationship between the margin status or width of negative margins and recurrence.[3] In the presented case, recurrences occurred at different locations: initially in the mastectomy scar and adjacent to the fascia; and in the remaining recurrences, in the left axillary tail. However, the last recurrence presented different behaviour as it was located on the latissimus dorsi cutaneous flap – not on the mastectomy scar – which is one more aspect that makes this case intriguing.

Tumour size (large tumours) and mitotic activity (> 10 mitosis per 10 HPF) were reported to be independently associated with local recurrence.[3] Also, stromal overgrowth and cytological atypia were referred to in the literature as independent prognostic factors.[7] Recurrences and metastases of PT may consist of mesenchymal elements only.[2]

Radiotherapy (which was offered to this patient but refused), has been proven to decrease local recurrence in malignant and borderline PT at 10 years, although it does not seem to affect the overall survival.[8]

This case revealed a singular behaviour of PT, and emphasised the importance of an integrated clinical-, imaging- and pathology-based approach to establish an adequate follow-up strategy for PT.

References

1. Plaza MJ, Swintelski C, Yaziji H, Torres-Salichs M, Esserman LE. Phyllodes tumor: review of key imaging characteristics. Breast Dis. 2015;35(2):79-86.
2. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, editors. World Health Organization Classification of Tumours of the Breast. Lyon: IARC Press; 2012.
3. Sevinç A, Aksoy S, Durak M, Balci P. Is the extent of surgical resection important in patient outcome in benign and borderline phyllodes tumors of the breast? Turk J Med Sci. 2018;48(1):28-33.

4. Duman L, Gezer N, Balci P, et al. Differentiation between phyllodes tumors and fibroadenomas based on mammographic sonographic and MRI features. Breast Care (Basel). 2016;11(2):123-127.
5. Tan H, Zhang S, Liu H, et al. Imaging findings in phyllodes tumors of the breast. Eur J Radiol. 2012;81(1):e62-e69.
6. Yabuuchi H, Soeda H, Matsuo Y, et al. Phyllodes tumor of the breast: correlation between mr findings and histologic grade. Radiology. 2006;241(3):702-709.
7. Tan PH, Thike AA, Tan WJ, et al. Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. J Clin Pathol. 2012;65(1): 69-76.
8. Strode M, Khoury T, Mangieri C, Takabe K. Update on the diagnosis and management of malignant phyllodes tumors of the breast. Breast. 2017;33:91-96.