Received: 18 August 2021 | Accepted: 18 August 2021

DOI: 10.1111/ecc.13508

EDITORIAL

European Journal of Cancer Care WILEY

Rare cancers and cancer of unknown primary: Here's what you should know!

In this issue, we have a *Special Supplement* focusing on rare cancers and cancer of unknown primary (CUP). Of the almost 4 million new cancer cases in Europe per year (Ferlay et al., 2018), about 24% are rare cancers. Rare cancers are defined as those with an incidence of <6/100,000 people per year, according to the *Surveillance of Rare Cancer in Europe* (RARECARE) consortium (Gatta et al., 2011). CUP refers to a heterogeneous group of metastatic cancers, for which the primary site cannot be identified after diagnostic work-up (Fizazi et al., 2015; Rassy & Pavlidis, 2019). CUP represents about 3%–5% of all cancers; however, it ranks among the top six causes of cancer deaths in Western countries (Pavlidis & Fizazi, 2009; van de Wouw et al., 2002).

Both rare cancers and CUP produce several (clinical) challenges, compared to more common cancers, such as breast and prostate cancer. Besides the relative low number of incident cases, they share the absence of a typical, uniform cancer presentation (Komatsubara & Carvajal, 2016; Ray-Coquard et al., 2017). Reasons for the lack of progress and existing challenges are multifactorial and include among others: insufficient public awareness, limited experience and training of primary and secondary health care professionals, deficient screening options for early diagnosis, limited access to appropriate diagnostic and treatment services, and lack of (referral to) tailored supportive, psychosocial care (de Heus et al., 2021; Fernandez, 2007; Gatta et al., 2011).

Fortunately, far-reaching improvements can be accomplished, specifically by enhancing research activity, and related to this, targeted allocation of funds and resources. However, research—as the driving force for progress and solid evidence—has primarily focused on common cancers so far, as organising adequately powered studies is less complicated in these more prevalent patient groups. These factors have led to suboptimal diagnostic and treatment processes and poor outcomes. For example:

- 5-year survival for rare cancers (48.5%) is worse than for common cancers in adults (63.4%), and improvement in survival is smaller (Gatta et al., 2017);
- prognosis for CUP is notoriously poor, with a median survival of approximately 2–12 months (Hemminki, 2012);
- rare cancer patients are more often confronted with delayed or false diagnosis and late (or no) referral to a centre of expertise (CoE);
- rare cancer patients report higher levels of distress, insecurity, loneliness, social isolation, anxiety and an overall lower quality of life compared to common cancer patients (Bergerot et al., 2018; de Heus et al., 2021; Feinberg et al., 2013);
- centralisation of care for rare cancers and CUP (in CoE) is suboptimal, while this is crucial to reduce disparities between rare and common cancers.

Rare cancers and CUP collectively are not rare. In this *Special Supplement* of the *European Journal of Cancer Care* on rare cancer and CUP, we have brought together an assembly of studies and commentaries, focusing on challenges and problems these patients and (health care) professionals are facing. First of all, to increase awareness, but essentially, we still have so much ground to cover.

In an extensive systematic review, de Heus et al. (2021) included 57 qualitative and quantitative studies with the aim to summarise unmet supportive care needs of rare cancer patients throughout their disease trajectory, per rare cancer domain, and to identify predictive factors for these unmet needs. Patients most frequently reported unmet needs regarding information provision, psychological support and physical and daily living support. Identified predictors of unmet needs were younger age and higher levels of anxiety and neuroticism. The authors emphasise that health care professionals should be aware of the different unmet needs per rare cancer domain and that these unmet needs should be recognised and individually addressed, starting from diagnosis onwards.

In two studies, haematological cancer patients received particular attention. Lindman et al. (2021) developed a multimodal interdisciplinary rehabilitation program (HAPPY), specifically for patients treated with non-myeloablative allogeneic haematopoietic stem cell transplantation (NMA-HSCT). It is a major challenge for these patients to maintain physical and psychosocial functioning and a certain level of participation in society. Patients ($n = 30$) in the HAPPPY program reported mainly good quality of life, both pre-NMA-HSCT and at 12-month follow-up, despite of presence of ongoing symptoms, such as fatigue after NMA-HSCT, and low cardiorespiratory fitness, both at baseline and follow-up. Long-lasting rehabilitation support is recommended by the authors for this exceptionally frail patient group.

Bennink et al. (2021) aimed to explore, using qualitative methods, perspectives and experiences of haematological cancer patients, specifically multiple myeloma (MM) patients, and (health care) experts regarding return to work (RTW) and participation at work. Improvement in survival and disease control has created new perspectives for MM patients, making it more relevant to consider issues, such as

social functioning and work ability. Overarching themes drawn from the interviews with patients ($n = 9$) and experts ($n = 15$) included: (1) severity of MM diagnosis and treatment impacts upon RTW; (2) step-by-step reintegration facilitates RTW; (3) meaning of work differs between MM patients and experts; and (4) tailored counselling is lacking in experts. Especially patients with lower education, physical limitations and those in physically demanding jobs are expected to benefit from timely and tailored counselling from specialised RTW experts.

In two further studies, tumours in the gastrointestinal tract were investigated. Eichler et al. (2021) explored health-related quality of life (HRQoL) in 130 patients from 13 centres, with a gastrointestinal stromal tumour (GIST), compared to the general population, and in GIST patients receiving tyrosine kinase inhibitor (TKI) therapy. GISTs are soft tissue sarcomas that can be located in any part of the digestive system. The authors found a mean global HRQoL score of 63.3 (out of 100 points) in GIST patients and large differences, compared to the general population, regarding social functioning and diarrhoea, and moderate differences regarding financial difficulties, insomnia and emotional functioning. Patients receiving at least their second line of TKI therapy had the highest symptom loads and restrictions in their HRQoL.

Patients with gastroenteropancreatic neuroendocrine neoplasms (GEPNENs) generally have a lower HRQoL compared to the general population as well, due to symptoms associated with functioning tumours, as well as treatment-related symptoms. Ronde et al. (2021) performed a systematic review and meta-analysis, including 20 studies. The underlying aim was to provide clinicians easy access to up-to-date evidence on the advantages and disadvantages of available treatment options, as GEPNENs patients may favour HRQoL prospects over prolonged survival. The authors indicated that all explored treatments appeared beneficial for disease stabilisation, while maintaining stable global HRQoL. Yet, they found that high-quality HRQoL reporting in these patients was lacking.

Supportive care needs in patients with epithelioid hemangioendothelioma (EHE), a vascular sarcoma, were examined by Husson et al. (2021). About one third of EHE patients has high symptom burden. To be able to tailor supportive health care to highly symptomatic EHE patients, the authors explored data of 115 EHE patients from 20 countries, using the PROFILES registry. Supportive care needs were found in every domain, with the highest score for the psychological domain. Needs were associated with younger age, advanced disease stage and being diagnosed less than 5 years ago. Greater awareness among health care professionals and proper assessment of unmet needs is important, as health care professionals are experts in diagnosis and treatment, but not necessarily in addressing these needs.

Epithelioid sarcomas (ES) are an extremely rare and aggressive type of soft tissue sarcoma with heterogeneity in presentation and clinical behaviour, predominantly affecting younger adults. Alves et al. (2021) contributed to this *Special Supplement* on rare cancers and CUP with a commentary on the evolving management of ES. Diagnosis has become easier, through loss of expression of INI1; however, optimal management of advanced ES remains difficult with limited response to chemotherapy.

Prusak et al. (2021) qualitatively explored the psychosocial impact of living with mesothelioma from both the patients' and caregivers' perspectives. Mesothelioma is a rare cancer with a poor prognosis, caused by exposure to asbestos. Themes that emerged from the interviews showed that patients ($n = 10$) seemed to have an active coping style, which became evident in arrangements they made regarding their forthcoming death. Patients indicated that they did not utilise psychosocial support, even though they experienced problems, such as adaptation issues. Overall, they appeared to have a lack of knowledge of and awareness about what psychosocial support actually entails and described how they primarily dealt with symptoms and problems themselves, mainly through family support. Carers ($n = 5$) of mesothelioma patients commonly showed a passive coping style. It was found that the offer of psychosocial support to carers differed between peripheral and specialised hospitals, but that their need for this type of support was high.

The perspectives and experiences of health care professionals and other relevant stakeholders regarding psychosocial support and palliative care in mesothelioma patients and their relatives was assessed in a qualitative study by Frissen et al. (2021). Also, gaps in current health care and potential improvements were discussed. Participants ($n = 16$) emphasised in the interviews the importance of accurate, timely and well-balanced information provision, regarding psychosocial support and palliative care, for these patients. A tailored care approach, not only in CoE but in all hospitals, with fluent transitions between primary and secondary cancer care, and palliative care early on in the disease process, are recommended.

Shifting our focus towards CUP, one original study and two commentaries have been included in this *Supplement*. Grewcock et al. (2021) investigated whether a family history of cancer is associated with increased CUP risk. The possible role of genetic susceptibility and shared environmental factors, contributing to increase CUP risk, is hinted at by the extensive evidence for clustering of cancer within families across anatomical sites. Therefore, the authors performed a case cohort analysis using data from the Netherlands Cohort Study, which included a total of 963 CUP cases and 4,288 subcohort members. However, they showed that having a family history of cancer is not an independent risk factor of CUP. The only consistent, but not statistically significant, association observed was a moderately increased CUP risk in participants who reported a sibling with cancer compared to those who did not.

Ye et al. (2021) addressed head and neck cancers, specifically squamous cell carcinoma in cervical lymph nodes arising from an undetected primary tumour (SCCUP), in their commentary. Moreover, they emphasise that clinicians who treat head and neck cancer patients should be familiar with diagnostic approaches to SSCUP, and they highlight several techniques. They stress that meticulous work-up of the SCCUP patient is central to the management of these patients, as identification of the primary site improves overall survival.

Finally, Loef et al. (2021) stated in their commentary that you must know your enemy in order to win the war. In the case of CUP, it means we need more epidemiological data, in addition to immunological and molecular data, to speed up the slow progress in clinical results. To address CUP patients' extremely poor prognosis, the authors propose a diagnostic work-up of patients with a cancer that is not immediately classifiable. The ultimate goal is enhanced survival of CUP patients.

As developments in common cancers have shown a steady and continuous progress over the years, collaborative, (inter)national efforts are needed to make up lost ground in rare cancers and CUP. Funds must be allocated to these unique patients groups. Not only to reduce existing inequalities with more prevalent cancers. Rare cancers and CUP might serve as experimental field for advances in personalized treatment in common cancers as well. By shifting our attention, the *future* rare cancer or CUP patient ideally will:

- be early detected and correctly diagnosed, potentially by using genome sequencing techniques,
- have appropriate access to and receive optimal treatment in a designated CoE, as part of a widely recognised (inter)national network between centres across the EU (and beyond),
- be referred for an (cross-border) expert or second opinion to a CoE, in case the diagnostic and/or treatment process necessitates this,
- be enrolled in clinical studies (e.g., to speed up development of new treatment options), as volume-related challenges for study participation have been overcome by introduction of new methodologies and by data linkage between high-quality (cancer) registries,
- experience better quality of life, because of tailored, psychosocial and supportive care for unmet needs throughout the disease trajectory and
- be able to connect with peers and obtain support; the tumour type of this particular patient might be rare, but they need to not feel they are alone.

We hope this selection of original studies and commentaries we have presented on rare cancers and CUP will be useful to health care professionals and researchers. Let us make this *future* patient tomorrow's reality!

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

KEYWORDS

cancer of unknown primary, expertise, organisation of care, patients, rare cancer

Saskia F. A. Duijts[1,2]
Jan Maarten van der Zwan[1]

[1]*Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands*
[2]*Amsterdam University Medical Centers, Amsterdam, The Netherlands*

Correspondence
Saskia Duijts, Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands;
Amsterdam University Medical Centers, Amsterdam, The Netherlands.
Email: s.duijts@iknl.nl

ORCID

Saskia F. A. Duijts https://orcid.org/0000-0001-6025-5361

REFERENCES

Alves, A., Constantinidou, A., Thway, K., Fisher, C., Huang, P., & Jones, R. L. (2021). The evolving management of epithelioid sarcoma. *European Journal of Cancer Care*, *30*, e13489. https://doi.org/10.1111/ecc.13489

Bennink, C., van der Klift, M., Scheurer, H., Sonneveld, P., & Duijts, S. F. A. (2021). Perspectives on returning to work of multiple myeloma patients: A qualitative interview study. *European Journal of Cancer*, *21*, e13481. https://doi.org/10.1111/ecc.13481

Bergerot, C. D., Bergerot, P. G., Philip, E. J., de Domenico, E. B. L., Manhaes, M. F. M., Pedras, R. N., Salgia, M. M., Dizman, N., Ashing, K. T., Li, M., Dale, W., & Pal, S. K. (2018). Assessment of distress and quality of life in rare cancers. *Psycho-Oncology*, *27*(12), 2740–2746. https://doi.org/10.1002/pon.4873

Feinberg, Y., Law, C., Singh, S., & Wright, F. C. (2013). Patient experiences of having a neuroendocrine tumour: A qualitative study. *European Journal of Oncology Nursing*, *17*(5), 541–545. https://doi.org/10.1016/j.ejon.2013.02.003

Ferlay, J., Colombet, M., Soerjomataram, I., Dyba, T., Randi, G., Bettio, M., Gavin, A., Visser, O., & Bray, F. (2018). Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *European Journal of Cancer*, *103*, 356–387. https://doi.org/10.1016/j.ejca.2018.07.005

Fernandez, C. V. (2007). Our moral obligations in caring for patients with orphan cancers. *CMAJ*, *176*(3), 297–299. https://doi.org/10.1503/cmaj.061623

Fizazi, K., Greco, F. A., Pavlidis, N., Daugaard, G., Oien, K., Pentheroudakis, G., & ESMO Guidelines Committee. (2015). Cancers of unknown primary site: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, *26*(Suppl 5), v133–v138. https://doi.org/10.1093/annonc/mdv305

Gatta, G., Capocaccia, R., Botta, L., Mallone, S., de Angelis, R., Ardanaz, E., Comber, H., Dimitrova, N., Leinonen, M. K., Siesling, S., van der Zwan, J. M., Van Eycken, L., Visser, O., Žakelj, M. P., Anderson, L. A., Bella, F., Kaire, I., Otter, R., Stiller, C. A., … RARECAREnet Working Group. (2017). Burden and centralised treatment in Europe of rare tumours: Results of RARECAREnet—A population-based study. *The Lancet Oncology*, *18*(8), 1022–1039.

Gatta, G., van der Zwan, J., Casali, P. G., Siesling, S., Dei Tos, A. P., Kunkler, I., Otter, R., Licitra, L., Mallone, S., Tavilla, A., Trama, A., Capocaccia, R., & RARECARE working group. (2011). Rare cancers are not so rare: The rare cancer burden in Europe. *European Journal of Cancer*, *47*(17), 2493–2511. https://doi.org/10.1016/j.ejca.2011.08.008

de Heus, E., Engelen, V., Dingemans, I., Richel, C., Schrieks, M., van der Zwan, J. M., Besselink, M. G., van Berge Henegouwen, M. I., van Herpen, C. M. L., & Duijts, S. F. A. (2021). Differences in health care experiences between rare cancer and common cancer patients: Results from a national cross-sectional survey. *Orphanet Journal of Rare Diseases*, *16*(1), 1–9.

Eichler, M., Pink, D., Menge, F., Jakob, J., Hentschel, L., Richter, S., Hohenberger, P., Kasper, B., Andreou, D., Singer, S., Grützmann, R., Dmytrow, D. I., Arndt, K., Tuchscherer, A., Reichardt, P., Ahrens, M.,

Kunitz, A., Mohm, J., & Schuler, M. K. (2021). Quality of life of GIST patients with and without current tyrosine kinase inhibitor treatment: Cross-sectional results of a German multicentre observational study (PROSa). *European Journal of Cancer Care*, *30*, e13484. https://doi.org/10.1111/ecc.13484

Frissen, A. R., Burgers, S., van der Zwan, J. M., Raijmakers, N., Arber, A., & Kunst, P. (2021). Experiences of healthcare professionals with support for mesothelioma patients and their relatives: identified gaps and improvements for care. *European Journal of Cancer Care*, *30*, e13509. https://doi.org/10.1111/ecc.13509

Grewcock, A. L. R., Hermans, K. E. P. E., Weijenberg, M. P., van den Brandt, P. A., Loef, C., Jansen, R. L. H., & Schouten, L. J. (2021). Family history of cancer in first degree relatives and risk of cancer of unknown primary. *European Journal of Cancer Care*, *30*, e13485. https://doi.org/10.1111/ecc.13485

Hemminki, K., Bevier, M., Hemminki, A., & Sundquist, J. (2012). Survival in cancer of unknown primary site: population-based analysis by site and histology. *Annals of oncology*, *23*(7), 1854–63.

Husson, O., Weidema, M., Leonard, H., DeYoung, L. H., van der Graaf, W., & van de Poll- Franse, L. (2021). Supportive care needs of patients living with an extremely rare and unpredictable cancer: The Epithelioid Haemangioendothelioma patient experience. *European Journal of Cancer*,*30*, e13461. https://doi.org/10.1111/ecc.13461

Komatsubara, K. M., & Carvajal, R. D. (2016). The promise and challenges of rare cancer research. *The Lancet Oncology*, *17*(2), 136–138. https://doi.org/10.1016/S1470-2045(15)00485-4

Lindman, A., Handberg, C., Olesen, G., & Duijts, S. (2021). Health-related quality of life and physical functioning in patients participating in a rehabilitation programme, undergoing non-myeloablative allogeneic haematopoietic stem cell transplantation: Outcomes from a single arm longitudinal study. *European Journal of Cancer*, *30*, e13478. https://doi.org/10.1111/ecc.13478

Loef, C., & Merkx, M. A. W. (2021). Cancer of unknown primary origin; Know the enemy. *European Journal of Cancer*, *30*, e13460. https://doi.org/10.1111/ecc.13460

Pavlidis, N., & Fizazi, K. (2009). Carcinoma of unknown primary (CUP). *Critical Reviews in Oncology/Hematology*, *69*, 271–278. https://doi.org/10.1016/j.critrevonc.2008.09.005

Prusak, A., van der Zwan, J. M., Aarts, M. J., Arber, A., Cornelissen, R., Burgers, S., & Duijts, S. F. A. (2021). The psychosocial impact of living with mesothelioma: Experiences and needs of patients and their carers regarding supportive care. *European Journal of Cancer*, *30*, e13498. https://doi.org/10.1111/ecc.13498

Rassy, E., & Pavlidis, N. (2019). The currently declining incidence of cancer of unknown primary. *Cancer Epidemiology*, *61*, 139–141. https://doi.org/10.1016/j.canep.2019.06.006

Ray-Coquard, I., Pujade Lauraine, E., Le Cesne, A., Pautier, P., Vacher Lavenue, M. C., Trama, A., & Blay, J. Y. (2017). Improving treatment results with reference centres for rare cancers: Where do we stand? *European Journal of Cancer*, *77*, 90–98. https://doi.org/10.1016/j.ejca.2017.02.006

Ronde, E. M., Heidsma, C. M., Eskes, A. M., Eskes, J. E., & Nieveen van Dijkum, E. J. M. (2021). Health-related quality of life and treatment effects in patients with well-differentiated gastroenteropancreatic neuroendocrine neoplasms: A systematic review and metaanalysis. *European Journal of Cancer Care*, *30*, e13504. https://doi.org/10.1111/ecc.1350

van de Wouw, A. J., Janssen-Heijnen, M. L., Coebergh, J. W., & Hillen, H. F. (2002). Epidemiology of unknown primary tumours; incidence and population-based survival of 1285 patients in Southeast Netherlands, 1984-1992. *European Journal of Cancer*, *38*, 409–413. https://doi.org/10.1016/S0959-8049(01)00378-1

Ye, W., Arnaud, E. H., Langerman, A., Mannion, K., & Topf, M. C. (2021). Diagnostic approaches to carcinoma of unknown primary of the head and neck. *European Journal of Cancer Care*, *30*, e13459. https://doi.org/10.1111/ecc.13459