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Clinical and pathological features of Merkel cell carcinoma: A 4-year follow-up observational retrospective study in Spain

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ABSTRACT

Background: Merkel cell carcinoma (MCC) is a malignant skin cancer with a 5-year survival rate of approximately 50%. Knowledge of MCC has increased in recent years mostly due to improved diagnosis techniques. In Spain there is lack of information regarding the incidence and tumour characteristics, and the treatment approaches are

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not standardised. The objective of this study was to provide information of the clinical and epidemiological characteristics of MCC patients in Spain.

Methods: Retrospective, observational study involving 192 patients from 25 Spanish hospitals. Evaluated variables included overall survival and incidence rate of Merkel cell polyomavirus, in patients diagnosed from 2012 to 2016.

Results: The Spanish incidence rate was estimated 0.32/100,000 inhabitants/year, with variations according to geographical regions, being slightly higher in areas with greater sunlight exposure. In total, 61.5% of tumours showed expansive growth (progressive growth of the tumour), 78.6% showed localisation in UV-exposed skin. 97.4% of patients were diagnosed by excisional biopsy. Surgery was the first line treatment in 96.6% of patients, radiotherapy in 24.6%, and chemotherapy in 6.3%. These treatments were not mutually exclusive. Median overall survival was 38.3 months (78.4% at 12 months and 60% at 24 months). MCPyV was present in 33.8% of patients.

Conclusion: The incidence of MCC in Spain is one of the highest in Europe, with a slight predominance in men. The sample has shown that a biopsy is available for diagnosis in most cases. Moreover, the treatment is surgical when the tumour is localized and is associated with lymphadenectomy, and/or it is radiotherapy if widespread.

1. Introduction

Merkel cell carcinoma (MCC) is an aggressive primary cutaneous neuroendocrine carcinoma that frequently metastasizes [1]. The spread of MCC is a predictive factor of 5-year overall survival, with estimates of 51%, 35% and 14% for local, nodal and distant disease [2]. MCC is twice as lethal as malignant melanoma [3]. Historically the therapeutic options for these patients have been limited; however, new immunotherapeutic approaches have shown durable responses [4]. Clinically, MCC presents as a rapidly growing red-violet, firm and painless cutaneous nodule in sun-exposed areas, i.e., head, neck and upper limbs [5]. These manifestations can be commonly diagnosed as benign cysts or as other kinds of benign tumours [6]. The clinical features associated with MCC are summarized in the AEIOU acronym: asymptomatic, expanding rapidly, immune suppression, older than 50 and UV-exposed site on a person with fair skin [7]. In a study where these characteristics were reviewed it was reported that out of 195 patients, 89% had three or four of these characteristics [6]. Although uncommon, the incidence of this type of tumour has increased fivefold over the past 30 years. For instance in United States in 1986 the incidence was 1.5 cases per million whereas in 2011 it raised up to 7.9 cases per million [1]. The increased in registered cases are partly due to improved diagnostic techniques (such as the introduction of cytokeratin-20 as an immunohistochemical diagnostic aid tool [1]) and clinical awareness [5]. This incidence rate is also attributed to the progressive aging of the population, the higher prevalence of risk factors (T-cell immune suppression) [5] and a high exposure to the sun [6]. One of the most important milestones in the knowledge of Merkel cell carcinoma's aetiology was the discovery of the Merkel cell polyomavirus (MCPyV). This polyomavirus appears in about 70–80% of the cases of MCC by immunohistochemical detection [1], but the prevalence is highly dependent on solar exposure, being higher in North America (69%) than in Australia (24%) [8]. In virus-positive tumours, whole transcriptome and genome sequencing of tumours have evidenced overlap of viral integration sites with focal genome amplifications [7]. Despite all the improvements in the comprehension and management of the disease, the incidence and tumour features are not well documented in Spain. Currently, the available data are from a regional registry (Girona) with a very small population [9], and from a systematic review and meta-analysis focused on the incidence and mortality of cutaneous cancer [10]. In addition, the clinical practice does not imply a multidisciplinary approach and treatments are not sufficiently standardized. The objective of the present study was to provide information of the clinical and epidemiological characteristics of MCC patients in Spain.

2. Material and methods

2.1. Study design

This was an epidemiologic, multi-centre, observational and retrospective study consisting of one cohort of patients diagnosed with Merkel cell carcinoma in 25 hospitals in Spain between 2012 and 2016, and that were willing to participate and share these data voluntarily. Data was collected by reviewing the clinical history of patients with Merkel cell carcinoma, from diagnosis till death due to any cause. Concomitant medication data were collected, although it was not considered as an exposure factor to be investigated, only described and analysed. Reviewing was made up until Dec. 2018. The main specialists who reviewed the clinical histories were pathologists, although others were also included (dermatologists, oncologists and surgeons).

Patients were included if they were aged $\geq$ 18 years old at the time of diagnosis of MCC, and pathologically confirmed as MCC at any stage and under any clinical condition between 2012 and 2016. Additionally, patients had to consent to participate in the study. On the other hand, patients were excluded if they did not have available data regarding disease course and concurrent treatments.

The study was conducted in accordance with the requirements of data protection rules established in the Guidelines for Ethical Review of Epidemiological Studies (Council for the International Organizations of Medical Sciences –CIOMS-, Ginebra, 1991), as well as in the Helsinki Declaration (Seoul, October de 2008). Protection and confidentiality of data were guaranteed according to the Organic Law 15/1999, 13 of December. The study abides by the rules dictated in the Ministry Order SAS/3470/2009 about observational studies developing.

2.2. Endpoints and variables

The primary objective was to determine the clinical and epidemiological characteristics of MCC patients in Spain. These features include: age, gender, comorbidities, geographic distribution, immunosuppression (recalling other causes, apart from transplants, lymphoma, HIV, etc), pathological characteristics and stage. Secondary objectives were to gather information regarding diagnosis processes, therapeutic approaches applied, and their results; to assess overall survival (OS), and to determine the incidence rate of MCPyV infection in an MCC cohort.

Immunohistochemistry with anti MCPyV large T-antigen antibody (CM2B4; mouse monoclonal antibody) diluted to 1:50 (Santa Cruz Biotechnology, USA) was performed for the detection of MCPyV in the Virgen Macarena Hospital by the same pathologist. It was performed on a histological section of a representative block of each neoplasm, using a positive immunostaining control on the same holder. Antigenic unmasking was used by heating for 30 min, prior to performing the IHC technique.

2.3. Estimation of sample size

Currently there are not robust data about incidence of MCC in Spain, since there is not a global national tumour registry. The only data is coming from a regional registry with a very small population, and it states that there are 0.31 MCC cases/100,000 inhab./year [9]. The incidence was calculated from the reference population of each hospital center. Due to the lack of information, we did a feasibility survey approaching 10 of the 25 study sites and made an approximation to the cases, obtaining an incidence rate of 0.33 MCC cases /100,000 inhab./year. Supposing a homogeneous distribution with a mean incidence in Spain (IR 0.31), we would expect to have around 144 new cases of MCC every year.

As an exploratory study and with the above information, there would be around 720 new MCC patients in 5 years. That means that we estimated that data of 200–250 patients diagnosed in the period of 2012–2016 are available, considering that the 25 participating centres have a population average of 580,000 inhabitants per site (based on the feasibility approach).

2.4. Statistical analysis

Overall survival (OS) was calculated from time of diagnosis of MCC and its analysis was summarized using Kaplan-Meier method. Patients without an event, defined as death or progression, were censored at the last date known to be alive for OS. The curve was plotted using 95% CI. Categorical variables were expressed as absolute and relative frequencies, and continuous ones as a mean, median, standard deviation (SD), and/or interquartile range (IQR). Statistical significance was established with $p < 0.05$.

3. Results

3.1. Study patients

In total 200 patients were included in the study from December 2018 to February 2020. However, 8 patients were excluded since the diagnosis date was outside the stipulated period (2012–2016). Therefore, a total of 192 patients were analysed. The global incidence across Spain was 0.32/100,000 inhabitants, quite close to the previously estimated data (0.33 MCC cases /100,000 inhabitants/year). Grouping by geographical areas, there is a higher incidence in the northern or east region (0.46/100,000 and 0.34/100000 inhabitants respectively) than in the central or southern areas (0.28/100,000 inhabitants in both cases). For further information on this regard, see Supplementary Table 1.

3.2. Primary endpoints

On average, the patient was diagnosed at the age of 78.9 years (SD: 12.6). There was a slightly higher incidence in males than in females (54.2% vs 45.8%) and most of the patients were Caucasian (92.7%, Table 1). Focusing on medical history, the incidence of comorbidities was the following ranging from more to less common: 35.4% exposure to ultraviolet radiation; 29.7% previous skin neoplasm; 7.3% immunosuppression; 6.8% autoimmune disease; 4.2% chronic lymphocytic leukaemia; 4.2% B-cell lymphomas; 3.1% solid organ transplantation and 0.5% HIV. The characteristics of the tumours differed among patients: 78.6% of patients had the tumour localized in UV-exposed/fair skin; 61.5% had an expansive growth of tumour; 61.5% were asymptomatic and 31.3% had other tumours (Table 1). Finally, 97.4% of patients had a diagnosis surgical biopsy. Median tumour size was 26.2 mm (SD: 25.9), mean tumour thickness was 18.4 mm (SD: 26.4) and mean mitotic index was 22.4 mitoses/mm^2 (SD: 23.1). A total of 38.0% of patients had an involvement of the lateral and/or deep margins, 32.6% lymphocytic inflammatory infiltration, 26.2% lymphovascular invasion.

Table 1
Sociodemographic and clinical characteristics of patients.

	Patients (N = 192)
Gender, n (%)	
Male	104 (54.2)
Female	88 (45.8)
Age, mean years (SD)	78.9 (12.6)
Race, n (%)	
Caucasian	178 (92.7)
Unknown	14 (7.3)
Stage TNM2010 T: Primary Tumour, n (%)	n = 133
T1: < 2 cm	64 (48.1)
T2: 2–5 cm	54 (40.6)
T3: > 5 cm	5 (3.8)
T4: Tumour has invaded the bone, muscle, fascia, or cartilage	10 (7.5)
Stage TNM2010 N: Regional Lymph Nodes, n (%)	n = 133
N0: No metastasis in nearby lymph nodes	90 (67.7)
N1a: Micrometastasis	7 (5.3)
N1b: Macrometastasis	29 (21.8)
N2: In-transit metastasis	7 (5.3)
Stage TNM2010 M: Metastasis, n (%)	n = 133
M0: No distant metastasis	116 (87.2)
M1a: Metastasis to the skin, tissues under the skin, or distant lymph nodes	6 (4.5)
M1b: Metastasis to the lung	2 (1.5)
M1c: Metastasis to any other internal organs	9 (6.8)
Medical history, n (%)	
Autoimmune disease	13 (6.8)
Solid organ transplantation	6 (3.1)
HIV	1 (0.5)
Chronic lymphocytic leukaemia	8 (4.2)
B-cell lymphomas	8 (4.2)
Previous skin neoplasm	57 (29.7)
Exposure to ultraviolet radiation	68 (35.4)
Immunosuppression	14 (7.3)
Clinical characteristics of MCC, n (%)	
Asymptomatic	118 (61.5)
Expansive growth	118 (61.5)
UV-exposed/fair skin	151 (78.6)
Other tumours	60 (31.3)
Diagnosis biopsy	
Tumour size, mean mm (SD)	26.2 (25.9)
Tumour thickness, mean mm (SD)	18.4 (26.4)
Mitotic index, mean mitoses/mm^2 (SD)	22.4 (23.1)

SD, standard deviation; HIV, human immunodeficiency virus; MCC, Merkel cell carcinoma; UV, ultraviolet

Additionally, 24.5% patients had lymphadenopathy, 9.6% extracutaneous extension, and 5.7% metastasis.

3.3. Secondary endpoints

Regarding the initial approaches and the management of the lymph nodes, an excisional biopsy was performed in 84.4% of the patients, an incisional biopsy/punch in 30.2% and a sentinel node biopsy in 17.7%. Surgery margins were affected in a high percentage (38%). Mean number of lines of treatment was 1.2, with surgery being the first line treatment in 96.6% of the cases, radiotherapy in 24.6% and chemotherapy in 6.3% (Table 2). These treatments were not mutually exclusive. Mean follow-up time was 24.1 months (SD: 21.9; range: 0–81). Along this time, 18.2% of patients had at least one lymphatic recurrence, 16.7% had at least one systemic relapse (metastasis), and 10.4% had at least one local recurrence. During the follow up period, 40.6% of the patients died resulting in a median survival time of 38.3 (95% CI: 29.2-not reached) months. The OS at 12 months was 78.4% (95% CI: 72.4–85.0) and at 24 months was 60.0% (95% CI: 52.6–68.4; Table 3 and Fig. 1). Incidence of MCPyV infection in this MCC cohort was 33.8% (CI 95%: 26.0 – 41.3). Grouping by geographical regions in Spain, in the southern region with higher exposition to UV, up to 80% of the patients were negative for the virus, whereas in the northern region the positive percentage was higher (40%), as shown in Supplementary Table 1.

Table 2
Therapeutic approaches.

	Patients (N = 192)
Management of the lymph nodes, n (%)	
Incisional biopsy/punch	58 (30.2)
Excisional biopsy	162 (84.4)
Sentinel node biopsy	34 (17.7)
Lymphadenectomy	20 (15.9)
Treatment lines	
Mean (range)	1.17 (0–5)
Description of treatments, n (%)	
First line of treatment	175 (91.1)
Surgery	169 (96.6)
Radiotherapy	43 (24.6)
Chemotherapy	11 (6.3)
Second line of treatment[a]	18 (16.4)
Surgery	2 (11.1)
Radiotherapy	10 (55.5)
Chemotherapy	5 (27.8)
Third line of treatment	5 (4.5)
Surgery	1 (20.0)
Radiotherapy	0 (0.0)
Chemotherapy	5 (100.0)

[a] Second line of treatment: after relapse or progression to first line.

Table 3
Patient's follow up.

	Patients (N = 192)
Patient time in the study, mean months (SD)	24.1 (21.9)
Situation at the end of follow-up, n (%)	
Alive	64 (33.3)
Deceased	78 (40.6)
Lost to follow up	50 (26.1)
Local recurrence (relapse), n (%)	20 (10.4)
Recurrences per patient, mean (SD)	0.1 (0.4)
Lymphatic recurrence, n (%)	35 (18.2)
Recurrences per patient, mean (SD)	0.3 (0.7)
Systemic relapse (metastasis), n (%)	32 (16.7)
Overall survival	
Median overall survival, months (95%CI)	38.3 (29.2 - NR)
At 12 months, % (95%CI)	78.4 (72.4 – 85.0)
At 24 months, % (95%CI)	60.0 (52.6 – 68.4)
At 60 months, % (95%CI)	44.7 (36.6 – 54.4)
Cause of death, n (%)	78 (40.6)
Disease progression	28 (35.9)
Infection	4 (5.1)
Cardiac disease	4 (5.1)
Kidney failure	3 (3.8)
Pneumonia	2 (2.6)
Complication after trauma	1 (1.3)
Postoperative	1 (1.3)
Respiratory failure	1 (1.3)
Unknown	34 (43.6)

SD, standard deviation; 95% CI, 95% confidence interval; NR, not reached

4. Discussion

4.1. Demographic data

There has been a growing incidence of MCC during the last three decades. Currently, the data available in countries with a high UV exposure like Australia or USA shows higher incidences, 1.6 per 100,000 inhabitants [11] and 0.79 cases/100,000 inhabitants respectively [1], followed by Europe, where The Surveillance of Rare Cancers in Europe (RARECARE) database reported an incidence of 0.13 per 100,000 [12]. Comparing this data with the Spanish rate (0.32/100,000 inhabitants), it is intriguing that the incidence is one of the highest in Europe, in accordance with the higher UV exposure, but far from the results in Australia. In this regard the National Cancer Data Base (spanning 1998–2012) concluded that MCC affects more older patients: up to 81.7% are in their 7th–9th decade of life, and mainly men (62.1%) [2]. In our study the data are in accordance, being the mean age 78.9 years, with a slight MCC predominance in males (54.2%) (1.2:1). The pathogenesis of MCC is related to a prominent of UV radiation [1], an idea supported by our study since it affects almost exclusively the white race (92.7%), localizes in photo-exposed areas (79.7%) and it is usually associated to other cutaneous tumours (29.7%). Furthermore, exposure to UV radiation (related to skin areas which are chronically exposed to sun) was recorded in 35.4% of total patients. In recent literature, immunosuppression is reported as a risk factor for developing MCC [1]. Patients with immune suppression due to hematologic malignancy, HIV, solid organ transplantation and autoimmune disease treatment have increased risk for developing this carcinoma. This trend is confirmed by our study, as 4.2% have hematological malignancies (CLL and lymphoma B), 0.5% HIV, 3.1% solid organ transplant and 6.8% autoimmune diseases. The frequency might be lower than expected, one possible explanation is that the use of inhibitors of BTK in the treatment of Lymphoma B has contributed to reduce the incidence of Merkel Cells carcinoma, although evidence to assert this is limited [13].

4.2. Diagnosis

The diagnosis of MCC is not always clinically suspected because the primary tumour lacks the typical features and is often asymptomatic. In this context, the pathological anatomy is key and therefore, the clinical report should include a meticulous examination such as the depth, tumour-infiltrating lymphocytes or tumour growth pattern. Additionally, when there is no clinically evident regional lymph node disease, it is recommended to perform a sentinel lymph node biopsy (SLNB) at the time of surgical excision of the primary MCC for staging and to appropriately manage the disease [1]. Within this context in our study we found that diagnosis was made by means of excisional biopsy (84.4%). The SLNB was relatively low (17.7%) since this is not a standard procedure in Spain. Large retrospective analyses or meta-analyses of SLNB in patients with clinically node-negative localised MCC have reported rates of SLN positivity between 30% and 38% [14,15].

4.3. MCC treatment and evolution

Two of the most important variables that predict the patient survival are the tumour size and the extend of the anatomic invasion [1]. In this study, the mean (SD) size of tumours was 26.2 (25.9) mm, that is T2 (2–5 cm). This is an important data because tumour size is the most important prognostic factor when it is localized, as is our series. N0 cases were 67.7% of patients, only 7.5% were T4. Also, most of the patients did not present distant metastasis at the diagnosis (87.2%, Table 2).

Large meta-analyses have reported that at least half of the patients with MCC develop lymph node metastases [16,17]. Additionally, nearly one third develop distant metastases with median time to recurrence between 8 and 9 months according to retrospective analyses [18,19]. In our study, the rates are lower than expected: 18.2% had at least one lymphatic recurrence, 16.7% had at least one systemic relapse (metastasis), 10.4% of the patients had at least one local recurrence (relapse). The mainstay of treatment for localized MCC is wide excision and adjuvant radiation [20]. For patients with clinically detectable regional lymph node metastases, options include completion lymphadenectomy and/or adjuvant radiation therapy [1]. In this scenario, in our series, surgery was the first line treatment in 96.6% of the patients (in accordance with first line practice), with radiotherapy in 24.6% and chemotherapy in 6.3%.

4.4. MCPyV incidence

The variability of the presence of MCPyV is inversely dependent on the solar exposition, which is related to geography. This fact explains

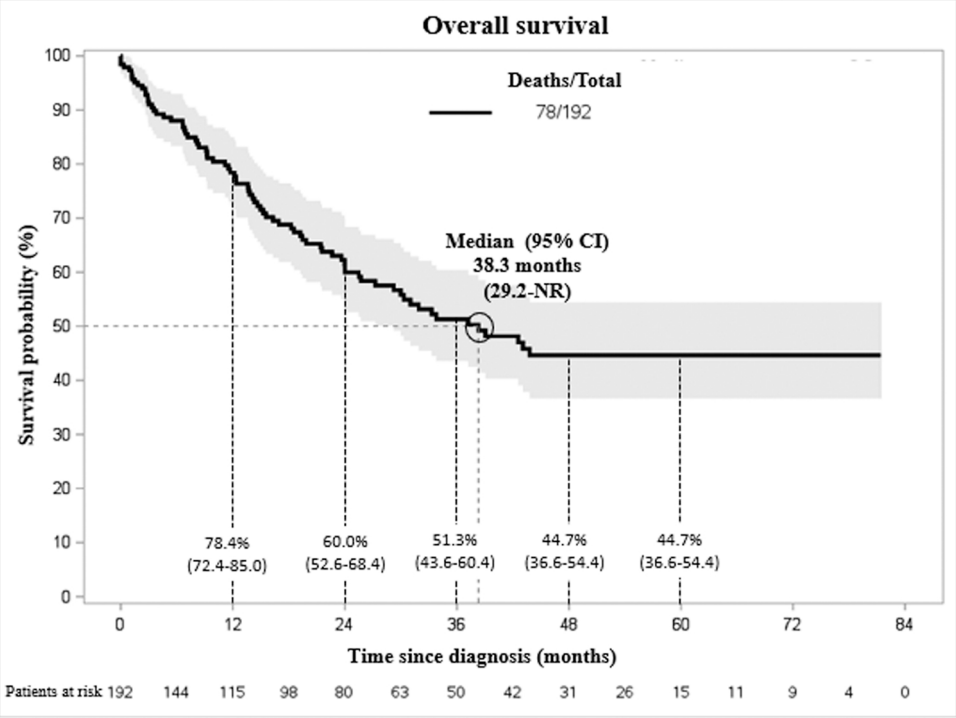

Fig. 1. Patient overall survival since diagnosis. NR: not reached.

that MCPyV incidence in Spain is 33.8%, lower than observed in North America (69%) and higher than in Australia (24%) [8].

5. Conclusions

The incidence of MCC in Spain is one of the highest in Europe, a fact probably related to a greater exposure to UV radiation. It has also been found a slight predominance in men. The sample has shown that an excisional biopsy is available for diagnosis in most cases. Moreover, the treatment is surgical when the tumour is localized and is associated with lymphadenectomy, and/or it is radiotherapy if widespread. The incidence of the MCPyV is in accordance with the expected values regarding the high solar exposition, with differences across the country.

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CRediT authorship contribution statement

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- Conceptualization.
- Methodology.
- Investigation.
- Data curation.
- Writing – reviewing and editing.
- Final draft.

Declaration of Interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2021.102081.

References

[1] M.T. Tetzlaff, P. Nagarajan, Update on merkel cell carcinoma, head and neck, Pathology 12 (2018) 31–43.
[2] K.L. Harms, M.A. Healy, P. Nghiem, A.J. Sober, T.M. Johnson, C.K. Bichakjian, S. L. Wong, Analysis of prognostic factors from 9387 merkel cell carcinoma cases forms the basis for the new 8th edition AJCC staging system, Ann. Surg. Oncol. 23 (2016) 3564–3571.
[3] D. Schadendorf, C. Lebbeé, A. Hausen, M.F. Avril, S. Hariharan, M. Bharmal, Merkel cell carcinoma: epidemiology, prognosis, therapy and unmet medical needs, Eur. J. Cancer 71 (2017) 53–69.

[4] N.M. Cassler, D. Merrill, C.K. Bichakjian, I. Brownell, Merkel cell carcinoma therapeutic update, Curr. Treat Opt. Oncol. 17 (2016) 36.
[5] R. Garcia-Carbonero, I. Marquez-Rodas, L. de la Cruz-Merino, J. Martinez-Trufero, M.A. Cabrera, J.M. Piulats, J. Capdevila, E. Grande, S. Martin-Algarra, A. Berrocal, Recent therapeutic advances and change in treatment paradigm of patients with merkel cell carcinoma, The Oncologist 24 (2019) 1375–1383.
[6] M. Heath, N. Jaimes, B. Lemos, A. Mostaghimi, L.C. Wang, P.F. Peñas, P. Nghiem, Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features, J. Am. Acad. Dermatol. 58 (2008) 375–381.
[7] Y. Xue, M. Thakuria, Merkel cell carcinoma review, Hematol. Oncol. Clin. N. Am. 33 (2019) 39–52.
[8] K.M. Garneski, A.H. Warcola, Q. Feng, N.B. Kiviat, J.H. Leonard, P. Nghiem, Merkel cell polyomavirus is more frequently present in North American than Australian Merkel cell carcinoma tumors, J. Invest. Dermatol. 129 (2009) 246–248.
[9] J. Rubió-Casadevall, A.M. Hernandez-Pujol, M.C. Ferreira-Santos, G. Morey-Esteve, L. Vilardell, G. Osca-Gelis, N. Vilar-Coromina, R. Marcos-Gragera, Trends in incidence and survival analysis in non-melanoma skin cancer from 1994 to 2012 in Girona, Spain: a population-based study, Cancer epidemiol. 45 (2016) 6–10.
[10] A. Tejera-Vaquerizo, M.A. Descalzo-Gallego, M.M. Otero-Rivas, C. Posada-García, L. Rodríguez-Pazos, I. Pastushenko, R. Marcos-Gragera, I. García-Doval, Incidencia y mortalidad del cáncer cutáneo en Espana: revisión sistemática y metaanálisis, Actas Dermosifiliogr 107 (2016) 318–328.
[11] J.C. Becker, A. Stang, J.A. DeCaprio, L. Cerroni, C. Lebbé, M. Veness, P. Nghiem, Merkel cell carcinoma, Nat. Rev. Dis. Primers 3 (2017) 17077.
[12] J.M. van der Zwan, A. Trama, R. Otter, N. Larrañaga, A. Tavilla, R. Marcos-Gragera, A.P. Dei Tos AP, E. Baudin, G. Poston, T. Links, Rare neuroendocrine tumours: results of the surveillance of rare cancers in Europe project, Eur. J. Cancer 49 (2013) 2565e78.
[13] D.A. Bond, Y. Huang, J.L. Fisher, A.S. Ruppert, D.H. Owen, E.M. Bertino, et al., Second cancer incidence in CLL patients receiving BTK inhibitors, Leukemia. 34 (2020) 3197–3205.
[14] T.I. Tarantola, L.A. Vallow, M.Y. Halyard, R.H. Weenig, K.E. Warschaw, T.E. Grotz, J.W. Jakub, R.K. Roenigk, J.D. Brewer, A.L. Weaver, C.C. Otley, Prognostic factors in Merkel cell carcinoma: analysis of 240 cases, J. Am. Acad. Dermatol. 68 (2013) 425–432.
[15] K. Mehrany, C.C. Otley, R.H. Weenig, P.K. Phillips, R.K. Roenigk, T.H. Nguyenet, A meta-analysis of the prognostic significance of sentinel lymph node status in Merkel cell carcinoma, Dermatol. Surg. 28 (2002) 113–117.
[16] D. Mercer, P. Brander, K. Liddell, Merkel cell carcinoma: the clinical course, Ann. Plast Surg. 25 (1990) 136–141.
[17] H. Medina-Franco, M.M. Urist, J. Fiveash, M.J. Heslin, K.I. Bland, S.W. Beenken, Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases, Ann. Surg. Oncol. 8 (2001) 204–208.
[18] A.C. Hui, A.L. Stillie, M. Seel, J. Ainslie, Merkel cell carcinoma: 27-year experience at the Peter MacCallum Cancer Centre, Int. J. Radiat Oncol. Biol. Phys. 80 (2011) 1430–1435.
[19] F.Q. Zhan, V.S. Sharon Packianathan, N.C. Zeitouni, Merkel cell carcinoma: a review of current advances, J. Natl. Compr. Cancer Netw. 1 (2009) 333–339.
[20] I. Prieto, T. Pérez-de-la-Fuente, M.S. Medina, B. Castelo, F. Cassinello, D. Esteban, N. Rodriguez-Salas, in: A. Riker (Ed.), Management of Non-melanoma Skin Cancers: Merkel Cell Carcinoma, Melanoma, Springer, Cham, 2018, pp. 623–636.