Postoperative Radiotherapy in Stage I-III Merkel Cell Carcinoma

Levy, Sonja; Blankenstein, Stephanie A; Jan Grünhagen, Dirk; Jalving, Mathilde; Hamming-Vrieze, Olga; Been, Lukas B; Tans, Lisa; van Akkooi, Alexander C J; Tesselaar, Margot E T

Published in:
Radiotherapy and Oncology

DOI:
10.1016/j.radonc.2021.11.017

Publication date:
2022

Radiotherapy and Oncology 166 (2022) 203–211

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Postoperative radiotherapy in stage I–III Merkel cell carcinoma

Sonja Levy [a,b,*,1], Stephanie A. Blankenstein [c,1], Dirk Jan Grünhagen [d], Mathilde Jalving [e], Olga Hamming-Vrieze [f], Lukas B. Been [g], Lisa Tans [h], Alexander C.J. van Akkooi [c,1], Margot E.T. Tesselaar [b,1]

[a] Department of Endocrine Oncology, University Medical Center Utrecht, ; [b] Department of Medical Oncology, Netherlands Cancer Institute; [c] Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, ; [d] Department of General Surgery, Erasmus Medical Center, Rotterdam; [e] Department of Medical Oncology, University Medical Center Groningen; [f] Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam; [g] Department of Surgical Oncology, University Medical Center Groningen; and [h] Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam

ARTICLE INFO

Article history:
Received 1 October 2021
Received in revised form 9 November 2021
Accepted 17 November 2021
Available online 25 November 2021

Keywords:
Merkel cell carcinoma
PORT
Radiotherapy
Survival

ABSTRACT

Background: Postoperative radiotherapy (PORT) is currently recommended for the treatment of Merkel cell carcinoma. Nevertheless, deviations occur frequently due to the generally elderly and frail patient population. We aimed to evaluate the influence of PORT on survival in stage I-III MCC patients treated in the Netherlands.

Methods: Patients were included retrospectively between 2013 and 2018. Fine-Gray method was used for cumulative incidence of recurrence and MCC-related death, cox regression was performed for overall mortality. Analyses were performed in patients with clinical (sentinel node biopsy [SN] not performed) stage I/II (c-I/II-MCC), pathologic (SN negative) stage I/II (p-I/II-MCC) and stage III MCC (III-MCC), separately. Propensity score matching (PSM) was performed to assess confounding by indication.

Results: In total 182 patients were included, 35 had p-I/II-MCC, 69 had c-I/II-MCC and 78 had III-MCC. Median follow up time was 53.5 (IQR 33.4–67.4), 30.5 (13.0–43.6) and 29.3 (19.3–51.0) months, respectively. Multivariable analysis showed PORT to be associated with less recurrences and reduced overall mortality, but not with MCC-related mortality. In stage III-MCC, extracapsular extension (subdistribution hazard [SDH] 4.09, $p = 0.012$) and PORT (SDH 0.45, $p = 0.044$) were associated with recurrence, and ≥ 4 positive lymph nodes (SDH 3.24, $p = 0.024$) were associated with MCC-related mortality.

Conclusions: PORT was associated with less recurrences and reduced overall mortality in patients with stage I-III MCC, but not with MCC-related mortality. Trends in overall survival benefit are likely to be caused by selection bias suggesting further refinement of criteria for PORT is warranted, for instance by taking life expectancy into account.

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine malignancy of the skin. The incidence of MCC is 0.5–0.8/100.000, but has been rising over the past decades [1,2]. With a median age of 75 years at diagnosis, it is predominantly a disease of the elderly [3–5]. The prognosis of patients strongly correlates with disease stage. Five-year overall survival (OS) for localized disease (stage I and II) was reported to be between 35–63% [5–7]. Up to 37% of patients present with nodal disease, which is associated with a five-year OS of 26.8–46.0% [5,6,8].

The mainstay of treatment for MCC consists of locoregional surgery. A wide local excision (WLE) of the primary tumor, accompanied by a sentinel lymph node biopsy (SN) in clinically node-negative disease, is recommended [9]. The National Comprehensive Cancer Network (NCCN) guidelines recommend – if appropriate after consultation within a multidisciplinary tumor board – a completion or therapeutic lymph node dissection (LND) (neck-dissection in case of MCC arising from the head and neck region), in case of microscopic or macroscopic nodal involvement, respectively [9]. Despite surgical efforts, the risk of recurrence is high [10,11]. Since MCC is generally considered to be very sensitive to radiotherapy, postoperative radiotherapy (PORT) has been implemented in the standard of care [12]. The NCCN guidelines recommend PORT in all primary MCC, although observation can be considered in widely excised, small primary tumors (<1 cm), and in the absence of other risk factors. PORT is also recommended when macro- or microscopically nodal disease led to LND, and more than 3 positive lymph nodes or extracapsular extension are found on pathological examination [9]. These guidelines are based on a retrospective analysis of 6908 cases, which showed an OS benefit in stage I and II treated with PORT, but not stage III MCC patients [13]. In the Netherlands, most patients with

* Corresponding author at: Heidelberglaan 100, 3584CX Utrecht, The Netherlands.
E-mail address: s.levy@umcutrecht.nl (S. Levy).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.radonc.2021.11.017
0167-8140/

MCC are treated in specialized referral centers. These centers work in close collaboration and treatment decisions are based on established evidence and guidelines.

Nonetheless, clinicians often deviate from the treatment protocols. This occurs because of physicians' or patients' preference, because patients are too frail to undergo treatment, or because the patients prognosis is defined by other comorbidities [14,15]. SN procedure is often omitted for similar reasons, which may lead to incomplete staging of disease and under-informed decision making [16]. For PORT, this has been illustrated in a recent study that investigated the concordance of PORT guidelines and treatment in MCC patients. The authors found that 57% of patients with a PORT indication were actually treated with radiotherapy. In these patients, PORT was associated with improved OS [15].

The guideline discordance in regard to staging and treatment, together with an often elder and frail population, makes it difficult to assess whether patients would benefit from adjuvant therapies, especially in retrospective analyses. In this study, we will evaluate the influence of PORT in patients with both clinically and pathologically defined stage I-III MCC, whilst controlling for confounding by indication in our analysis. Further, we will investigate the effect of PORT on different outcomes, namely recurrence, MCC-related mortality and overall survival. By doing so, we will be able to assess whether the frailty and non-MCC-related prognosis of patients are likely influencing treatment decision and survival outcomes.

Materials and Methods

Patient selection

Patients from three referral centers were included in this retrospective multicenter observational study, covering over three quarters of the Dutch MCC population. All patients with histologically proven stage I-III MCC, diagnosed between 2013 and 2018, and with an indication for PORT, were eligible for inclusion. This study was conducted according to the principles of the Declaration of Helsinki and approved by local Institutional Review Boards (IRBs). All patients gave consent for the use of their pseudo-anonymized medical data.

Objectives

The primary objective of this study was to investigate the influence of PORT on recurrence, MCC-related mortality and overall mortality of patients with stage I-III MCC. Recurrence was defined as time in months from initial histopathological diagnosis until documented first recurrence or death from MCC. MCC-related mortality was defined as time in months from the same initial time point until death from MCC. Patients that died from unknown causes but had stage IV disease at last follow up were considered to have died from MCC. Patients that died of comorbidities were considered as competing risks for both RFS and MCC-related mortality. Patients who were alive at the end of study were censored.

The secondary objective of this study was to identify predictors for recurrence, MCC-related mortality and overall mortality in stage I-III MCC patients.

Statistical analyses

Descriptive statistics were used to describe baseline characteristics: frequencies and percentages for categorical variables, medians with interquartile ranges (IQR) for continuous variables. Characteristics of patients who did and did not receive PORT were compared using the Fisher's exact test in categorical variables and Wilcoxon rank sum test in continuous variables.

Due to the observational nature of this study, the choice for PORT could be subject to differences in patient characteristics. Therefore, patients were matched using propensity score matching (PSM) to ensure two groups with equal characteristics associated with receiving PORT. One-to-*n* matching with replacement with the nearest Mahalanobis metrics matching was performed. The PORT group was used as reference group for matching. Propensity score was estimated by a logistic regression and covariates included in the propensity score were selected based on their contribution to PORT treatment decision. Covariates were gender, age, World Health Organization (WHO) performance score (PS), T stage, N stage, head and neck tumors (as binary variable, yes/no), radical excision (yes/no) and lymph-/angioinvasion (yes/no). The standardized mean difference was used to assess the balance of covariates after matching, a value of > 0.1 was used as a cut-off for imbalance of covariates.

For recurrence and MCC-related mortality competing risk analyses using the Fine-Gray method were performed. Cumulative incidence and Kaplan-Meier curves were plotted for visualization of recurrence, MCC-related and overall mortality. A multivariable Fine-Gray model was constructed for identification of independent predictors of recurrence and MCC-related mortality. Multivariable cox regression was performed for overall mortality. Predictors were selected according to clinical knowledge regarding their influence on survival, radiotherapy was included as predictor of interest. The sub-distribution hazards (SDH) were shown and can be interpreted in similar manner to hazard ratios (HR) in a cox proportional hazards model. To preserve statistical power, we included patients with missing values as 'unknown' categories in our multivariable analysis. A statistical probability (p-value) of < 0.05 was considered significant.

Analyses were performed using IBM SPSS, version 25 and R version 3.6.2. R packages 'survival', 'MatchIt', 'cmprsk' were used.

Results

A total of 218 patients with stage I-III were referred to the three expert centers in the study period. Of these, 182 had an indication for PORT according to current guidelines. Of the patients without a PORT indication, 2 (5.5%) received PORT. In contrast, 94 (51.6%) patients with a PORT indication did not receive PORT.

All further analysis were performed in the patients with a PORT indication. Median age was 73.8 years (IQR 66.8–81.1) and 80 patients (44.0%) were female. Thirty-five patients (19.2%) had pathological (SN negative) stage I/II MCC (p-I/II-MCC), 69 patients (37.9%) had clinical (SN not performed) stage I/II MCC (c-I/II-MCC), and 78 patients (42.9%) had stage III MCC (III-MCC). Baseline characteristics for all patients, the distribution according to disease stage and PORT are summarized in Table 1. Significant differences were found in the following characteristics: p-I/II-MCC patients treated with PORT more often had primary tumors of the head & neck (45.5% vs. 8.3%), whereas patients with a MCC of the extremity were less frequently treated with PORT (27.3 vs. 66.3, p = 0.023). In c-I/II-MCC, patients treated with PORT were older (81.9 years vs 77.1 years, p = 0.029). In patients with III-MCC, significant differences were mostly seen in pathological characteristics: patients treated with PORT had more unknown primary tumors (Tx) (24.4% vs. 12.1%) and larger tumors (T2 and T3) (37.8% vs. 21.2% and 11.1% vs. 6.1%, p = 0.034, respectively). Free excision margins had been achieved less frequently in the patients receiving PORT (86.7% vs. 100%, p = 0.032), SN-procedure was performed less often (26.7% vs. 54.5%, p = 0.018), but when additional lymph node dissection was performed, positive lymph nodes were found more frequently: 44.4% vs. 22.2% for 2–3 lymph nodes, and 29.9% vs. 9.1% for $\geq$ 4 lymph nodes (p = 0.011). Compared to

Table 1
Baseline characteristics of all patients across all three subgroups and PORT. PORT: postoperative radiotherapy, CCS: Charlson comorbidity score, PS: World Health Organization performance score, T: tumor, SN: sentinel node, LND: lymph node dissection.

Characteristic	All N (%)	Pathological Stage I/II				Clinical Stage I/II				Stage III			
		All	No PORT	PORT	*P*-value	All	No PORT	PORT	*P*-value	All	No PORT	PORT	*P*-value
Total	**182**	**35**	**24**	**11**		**69**	**37**	**32**		**78**	**33**	**45**	
Gender					0.146				0.811				0.346
Female	80 (44.0)	17 (48.6)	14 (58.3)	3 (27.3)		34 (49.3)	19 (51.4)	15 (46.9)		29 (37.2)	10 (30.3)	19 (42.2)	
Male	102 (56.0)	18 (51.4)	10 (41.7)	8 (72.7)		35 (50.7)	18 (48.6)	17 (53.1)		49 (62.8)	23 (69.7)	26 (57.8)	
Age *(median, range)*		69.9 (17.3-81.5)	70.7 (17.3-81.5	66.8 (48.9-81.2)	0.456	80.3 (54.3-94.8)	81.9 (59.8-84.7)	77.1 (54.3-94.6)	**0.029**	71.0 (41.9-89.6)	73.6 (41.9-85.4)	70.5 (44.4-89.6)	0.125
CCS					0.086				0.721				0.418
0	76 (41.8)	14 (40.0)	12 (50.0)	2 (18.2)		30 (43.5)	15 (40.5)	15 (46.9)		32 (41.0)	11 (33.3)	21 (46.7)	
1	53 (29.1)	14 (40.0)	9 (37.5)	5 (45.5)		16 (23.2)	8 (21.6)	8 (25.0)		23 (29.5)	10 (30.3)	13 (28.9)	
2	34 (18.7)	6 (17.1)	2 (8.3)	4 (36.4)		11 (15.9)	8 (21.6)	3 (9.4)		17 (21.8)	10 (30.3)	7 (15.6)	
3	15 (8.2)	1 (2.9)	1 (4.2)	0		8 (11.6)	4 (10.8)	4 (12.5)		6 (7.7)	2 (6.1)	4 (8.9)	
4	3 (1.6)	0	0	0		3 (4.3)	2 (5.4)	1 (3.1)		0	0	0	
5	0	0	0	0		0	0	0		0	0	0	
6	0	0	0	0		0	0	0		0	0	0	
7	0	0	0	0		0	0	0		0	0	0	
8	1 (0.5)	0	0	0		1 (1.4)	0	1 (3.1)		0	0	0	
PS					0.460				0.598				0.634
0	85 (46.7)	16 (45.7)	10 (41.7)	6 (54.5)		24 (35.1)	13 (35.1)	11 (34.4)		45 (57.7)	18 (54.5)	27 (60.0)	
1	60 (33.0)	15 (42.9)	12 (50.0)	3 (27.3)		27 (39.1)	14 (37.8)	13 (40.6)		18 (23.1)	9 (27.3)	9 (20.0)	
2	27 (14.8)	4 (11.4)	2 (8.3)	2 (18.2)		9 (13.0)	4 (10.8)	5 (15.6)		14 (17.9)	5 (15.2)	9 (20.0)	
3	7 (3.8)	0	0	0		6 (8.7)	5 (13.5)	1 (3.1)		1 (1.3)	1 (3.0)	0	
Unknown	3 (1.6)	0	0	0		3 (4.3)	1 (2.7)	2 (6.3)		0	0	0	
T-stage					0.550				0.116				**0.034**
T0	15 (8.2)	n/a	n/a	n/a		n/a	n/a	n/a		15 (19.2)	4 (12.1)	11 (24.4)	
T1: ≤1 cm	27 (14.8)	8 (22.9)	6 (25.0)	2 (18.2)		14 (20.3)	7 (18.9)	7 (21.9)		5 (6.4)	2 (6.1)	3 (6.7)	
T1: >1 cm & ≤2 cm	62 (34.1)	11 (31.4)	8 (33.3)	3 (27.3)		29 (42.0)	16 (43.2)	13 (40.6)		22 (28.2)	16 (48.5)	6 (13.3)	
T2: >2 cm & ≤5 cm	52 (28.6)	10 (28.6)	7 (29.2)	3 (27.3)		18 (26.1)	13 (35.1)	6 (15.6)		24 (30.8)	7 (21.2)	17 (37.8)	
T3: >5 cm	9 (4.9)	1 (2.9)	0	1 (9.1)		1 (1.4)	0	1 (3.1)		7 (9.0)	1 (6.1)	5 (11.1)	
T4	6 (3.3)	1 (2.9)	0	1 (9.1)		3 (4.3)	0	3 (9.4)		2 (2.6)	1 (3.0)	1 (2.2)	
Unknown	11 (6.0)	4 (11.4)	0	1 (9.1)		4 (5.8)	1 (2.7)	3 (9.4)		3 (3.8)	1 (3.0)	2 (4.4)	
Location primary					**0.023**				0.241				0.469
Head & Neck	78 (42.9)	7 (20.0)	2 (8.3)	5 (45.5)		49 (71.0)	23 (62.2)	26 (81.3)		22 (28.2)	9 (27.3)	13 (28.9)	
Trunk	30 (16.5)	9 (25.7)	6 (25.0)	3 (27.3)		9 (13.0)	6 (16.2)	3 (9.4)		12 (15.4)	5 (15.2)	7 (15.6)	
Extremity	59 (32.4)	19 (54.3)	16 (66.7)	3 (27.3)		11 (15.9)	8 (21.6)	3 (9.4)		29 (37.2)	15 (45.5)	14 (31.1)	
Unknown primary	15 (8.2)	n/a	n/a	n/a		n/a	n/a	n/a		15 (19.2)	4 (12.1)	11 (24.4)	
Excision margins					n/a				0.743				**0.032**
Margins free	165 (90.7)	35	24 (100)	11 (100)		58 (84.1)	32 (86.5)	26 (81.3)		72 (92.3)	33 (100)	39 (86.7)	
Margins not free	17 (9.3)	0	0	0		11 (15.9)	5 (13.5)	6 (18.8)		6 (7.7)	0	6 (13.3)	
SN-procedure					0.314				n/a				**0.018**
Negative	34 (18.6)	34 (97.1)	24 (100)	10 (90.1)						0	0	0	
Positive	30 (16.5)	0	0	0						30 (38.5)	18 (54.5)	12 (26.7)	
Not performed	118 (64.8)	1 (2.9)	0	1 (9.1)*		69	37 (100)	32 (100)		48 (61.5)	15 (45.5)	33 (73.3)	
Nodal status†													**0.011**
1 node positive	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	7 (9.0)	6 (18.2)	1 (2.2)	
2-3 nodes positive	n/a	n/a	n/a	n/a		n/a	n/a	n/a		31 (39.7)	11 (33.3)	20 (44.4)	
>3 nodes positive	n/a	n/a	n/a	n/a		n/a	n/a	n/a		16 (20.5)	3 (9.1)	13 (29.9)	
SN positive, LND not performed	n/a	n/a	n/a	n/a		n/a	n/a	n/a		20 (25.6)	12 (36.4)	8 (17.8)	
SN and LND not performed	n/a	n/a	n/a	n/a		n/a	n/a	n/a		4 (5.1)	1 (3.0)	3 (6.7)	

(*continued on next page*)

Table 1 (*continued*)

Characteristic	All N (%)	Pathological Stage I/II			*P*-value	Clinical Stage I/II			*P*-value	Stage III			*P*-value
		All	No PORT	PORT		All	No PORT	PORT		All	No PORT	PORT	
Extracapsular extension†													0.063
No	n/a	n/a	n/a	n/a		n/a	n/a	n/a		26 (33.3)	9 (27.3)	17 (37.8)	
Yes	n/a	n/a	n/a	n/a		n/a	n/a	n/a		19 (34.4)	5 (15.2)	14 (31.1)	
Unknown	n/a	n/a	n/a	n/a		n/a	n/a	n/a		33 (42.3)	19 (57.6)	14 (31.1)	
Lymph-/angioinvasion					0.422				0.264				**0.032**
No	50 (27.5)	14 (40.0)	8 (33.3)	6 (54.5)		18 (26.1)	7 (18.9)	11 (34.4)		18 (23.1)	6 (18.2)	12 (26.7)	
Yes	43 (23.6)	9 (25.7)	6 (25.0)	3 (27.3)		13 (18.8)	9 (24.3)	4 (12.5)		21 (26.9)	14 (42.2)	7 (15.6)	
Unknown	89 (48.9)	12 (34.3)	10 (41.7)	2 (18.2)		38 (55.1)	21 (56.8)	17 (53.1)		39 (50.0)	13 (39.4)	26 (57.8)	

* One patient was suspected of metastasis to parotid gland on imaging, sentinel node procedure not performed. Resection showed no metastasis. For analysis purposes this patient was further included in SN-negative group.
† Only applicable for stage III-MCC.

patients who did not receive PORT, lymph-/angioinvasion was found in less patients treated with PORT (15.6% vs. 42.2%), yet this was unknown in a larger proportion of patients with PORT (57.8% vs. 39.4%, p = 0.032). Patients without PORT more often had unknown extracapsular invasion status (57.6% vs. 31.1%, p = 0.063). Median follow up time for all patients was 34.6 months (IQR 18.3–55.5). For patients with p-I/II-MCC median follow up time was 53.5 months (IQR 33.4–67.4), for patients with c-I/II-MCC this was 30.5 months (IQR 13.0–43.6) and for patients with III-MCC this was 29.3 months (IQR 19.3–51.0).

PSM yielded 51:84 matched treated:control units. The PSM cohort showed highly similar effects for PORT compared to the unmatched cohort. Further analyses were therefore executed in the unmatched cohort to maximize power. Results of PSM and survival curves for original and matched cohort can be found in the supplementary material, Figure S1 and S2, respectively.

Considering all patients, 80 (44.0%) had recurrent disease. Of the 44 patients that received PORT of only the primary tumor (and not the nodal basin), recurrences were local in one (2.4%), regional in 14 (31.8%) and distant in three (6.8%) patients. In patients that received PORT of both the primary tumor and the nodal basin, all recurrences were distant (n = 12, 38.7%). Thirteen patients received PORT of nodal basin only, these were all patients with unknown primary tumors. Of these, one patient (7.7%) had a regional recurrence, and 5 (38.5%) had distant recurrences. Recurrences across local and/or regional PORT are summarized in Table 2. For illustration of local, regional or distant recurrences, cumulative incidence curves stratified by PORT are shown in Fig. 1.

Univariable competing risk analysis showed no difference in disease recurrence for patients treated or not treated with PORT in p-I/II-MCC (p = 0.590) and in c-I/II-MCC (p = 0.260). In patients with III-MCC, PORT was associated with less recurrences (p = 0.030). Cumulative incidence of recurrence curves are shown in Fig. 2a. Multivariable analysis of recurrence identified a higher disease stage: c-I/II-MCC had a SDH of 3.05 (p = 0.025), III-MCC had a SDH of 6.24 (p < 0.001) and PORT (SDH 0.59, p = 0.039) as independent predictors. Also, an unknown PS (SDH 5.33, p < 0.001) was significantly associated with recurrence, but this group only included 3 patients. To assess the influence of known nodal pathological characteristics on recurrence, multivariable analysis was repeated in III-MCC with inclusion of known risk factors for recurrence. Here, unknown lymph-/angioinvasion (SDH 0.29, p = 0.012), the presence of extracapsular extension (SDH 4.09, 0 = 0.012) and PORT (SDH 0.45, p = 0.044) were found to be independent predictors for recurrence (Table 4).

Regarding MCC-related mortality, Fine-Gray analysis did not show a significant difference for PORT in any of the three subgroups: p = 0.530, p = 0.430 and p = 0.980 for p-I/II-MCC, c-I/II-MCC and III-MCC, respectively. In the complete cohort, 13 (7.1%) patients died from other causes than MCC, two of whom died from a malignancy other than MCC. Cumulative incidence curves are found in Fig. 2b. Multivariable analysis identified male gender (SDH 2.21, p = 0.033), and disease stages c-I/II-MCC (SDH 4.84, p = 0.017) and III-MCC (SDH 7.12, p < 0.001) to be associated with MCC-related mortality (Table 3). Similar to the analysis of recurrence, unknown PS (SDH 6.13, p = 0.033) showed significant results. In multivariable analysis for III-MCC, only the presence of $\geq$ 4 lymph nodes was associated with MCC-related mortality (Table 4).

Kaplan-Meier curves and cox regression were performed for overall mortality. In patients treated with PORT a trend was seen towards improved survival in c-I/II-MCC (p = 0.076), and no difference was seen in p-I/II-MCC (p = 0.990) and III-MCC (p = 0.200). Kaplan-Meier curves for overall mortality are shown in Fig. 2c. Multivariable cox regression identified a PS of 2 (HR 2.23, p = 0.039), PS of 3 (HR 3.36, p = 0.044) and an unknown PS (HR

Table 2
Recurrences across local and/or regional postoperative radiotherapy (PORT).

	PORT			
	No PORT, n (%)	Primary tumor only, n (%)	Lymph nodes only, n (%)	Primary and lymph nodes,n (%)
No recurrence	50 (53.2)	26 (59.1)	7 (53.8)	19 (61.3)
Local	5 (5.3)	1 (2.3)	0	0
Regional	27 (28.7)	14 (31.8)	1 (7.7)	0
Distant	12 (12.7)	3 (6.8)	5 (38.5)	12 (38.7)
Total	94 (100)	44 (100)	13 (100)	31 (100)

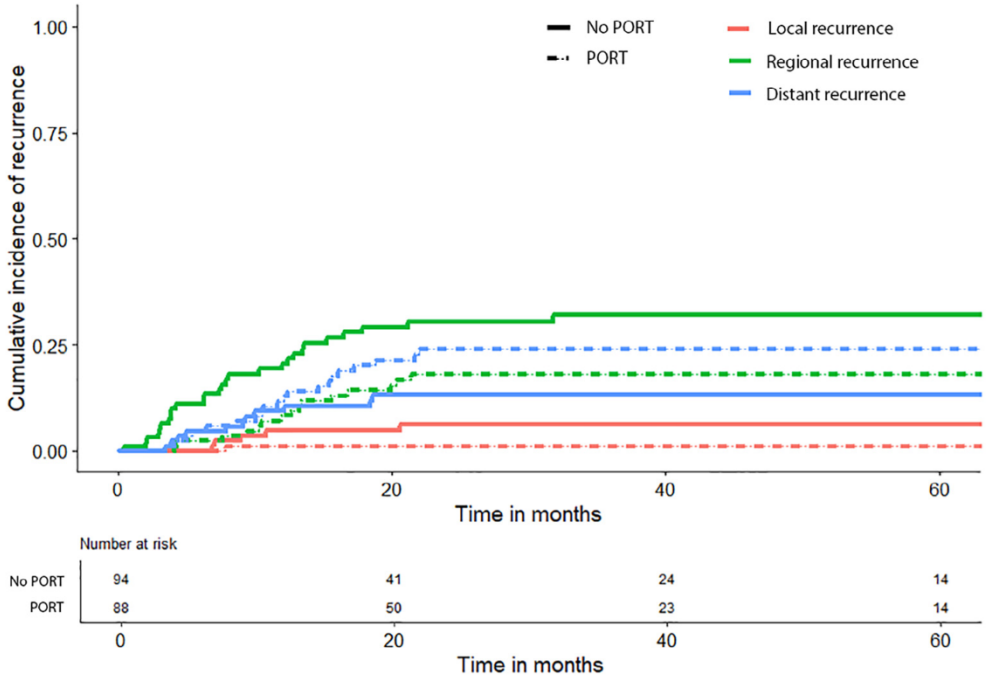

Fig. 1. Cumulative incidence curves for local, regional and distant recurrence. PORT: postoperative radiotherapy.

8.84, p = 0.002), primary tumor location on the trunk (HR 2.21, p = 0.039), more advanced disease stage: c-I/II-MCC (HR 4.92, p = 0.008) and III-MCC (HR 7.81, p < 0.001) and treatment with PORT (HR 0.52, p = 0.035) as significant predictors for overall mortality (Table 3). In III-MCC, a PS of 2 (HR 5.64, p = 0.003) and PORT (HR 0.37, p = 0.031) were associated with overall mortality (Table 4).

Discussion

In this large multicenter cohort of patients with stage I-III Merkel cell carcinoma we found that PORT was associated with less recurrences and reduced overall mortality across all stages, yet we found no difference for PORT in MCC-related mortality. Further, in stage III-MCC, we found that known prognostic factors such as extracapsular extension were associated with recurrence, and $\geq$ 4 positive lymph nodes with MCC-related death, respectively.

The benefit of PORT in the treatment of MCC has long been the subject of debate. In 2019, a meta-analysis summed available evidence of 29 studies that included PORT in MCC patients. Similar to our study, this study indicated that PORT seemed to be associated with improved disease-free and overall survival (OS) [17]. We found that PORT was associated with reduced overall mortality, but not with MCC-related mortality. This can be explained by the guideline-discordance that has been mentioned previously. In our cohort, 51.6% of patients did not receive PORT when this was indicated. Although the reasons for this are unknown, the reluctance to treat patients with PORT could be based on a pre-existent shorter life expectancy. This would explain the difference in overall and MCC-related mortality, indicating that patients who did not receive PORT were deemed more likely to die of other causes. If so, PORT was correctly withheld from these patients. A similar bias could have been present in the large study on which the current guidelines are based, and in other studies reported in aforementioned review [13,17]. Interestingly, we did not find an overall mortality benefit for PORT in patients with p-I/II-MCC, whereas Bhatia, et al. did [13]. Since this benefit potentially rises from an association with causes of death unrelated to MCC, it is possible that in their cohort more patients with stage I/II MCC died from other causes than MCC, compared the cohort in the current study.

Our results are similar to a number of studies that have investigated both MCC-specific survival and OS. For instance, after analyzing 269 propensity score matched pairs of patients with MCC, Kim, et al. concluded that the survival benefit of PORT may be due to selection bias or unmeasured confounders, and not PORT [18]. Similarly, this phenomenon was demonstrated in a recent analysis, where PORT was identified as a significant contributor to a nomogram for OS, but not to a nomogram for MCC-related survival, again suggesting possible selection bias [19]. Finally, in an analysis of patients with MCC > 65 years old, treatment with PORT was found to be associated with improved OS, but not MCC-specific survival [20]. The discrepancy between MCC-related survival and OS in these studies indicate that selection criteria for

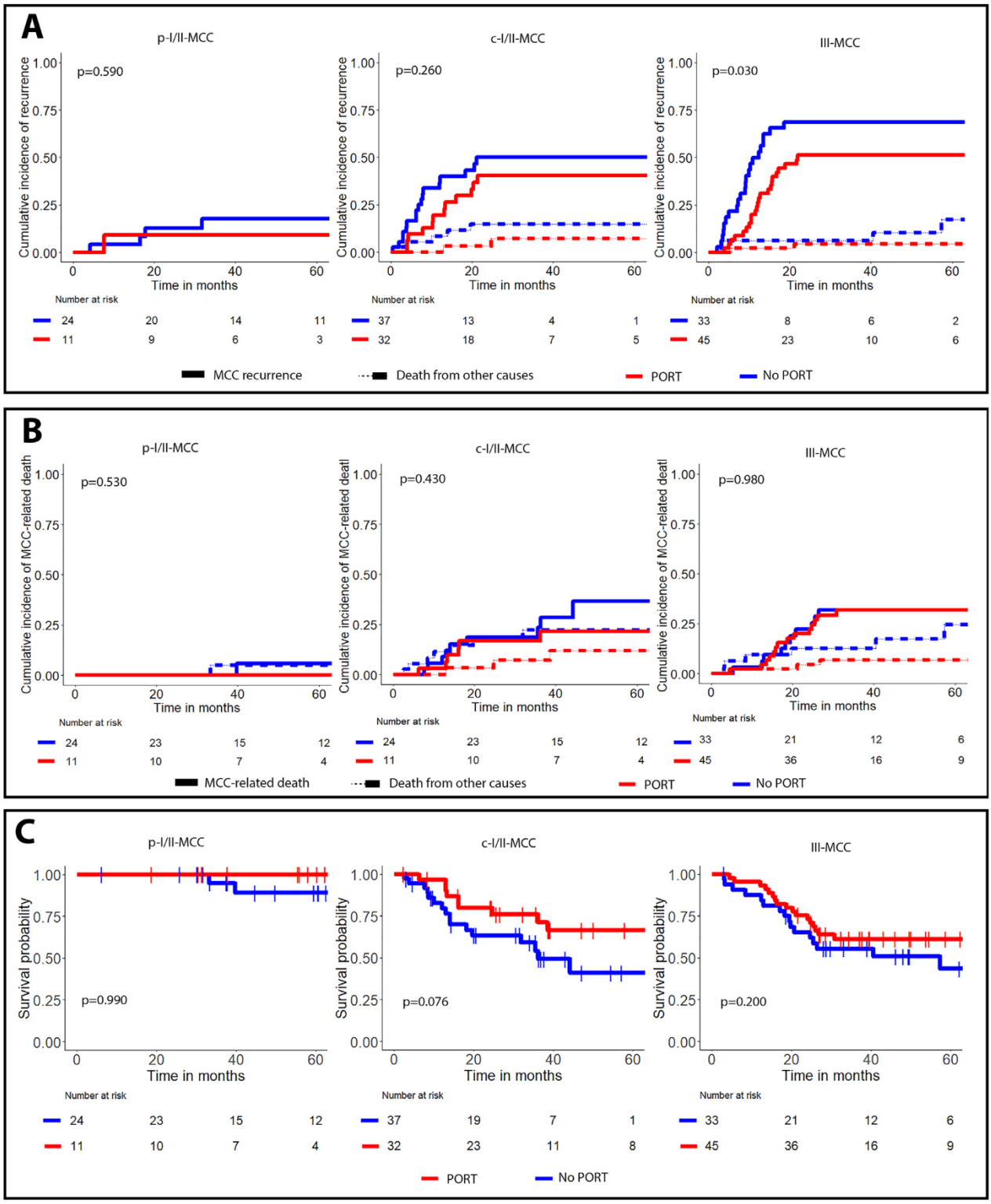

Fig. 2. A: Cumulative incidence of recurrence curves. B: Cumulative incidence curves for MCC-related death. C: Kaplan-Meier curves for overall survival. PORT: postoperative radiotherapy, MCC: Merkel cell carcinoma, p-I/II: pathological stage I/II, c-I/II: clinical stage, III: stage III.

PORT could be refined, for instance by taking life expectancy into account. The use of composite endpoints (combinations of multiple endpoints into one primary endpoint) is common in medical research, especially in clinical trials [21–23]. Yet the use of such endpoints should be judged critically, and when an outcome is (partly) associated with the exposure – as is the case with PORT and OS in patients with MCC – serious selection bias may occur [24]. Therefore studies investigating survival in patients with MCC, should include MCC-related survival, with or without OS outcomes.

Table 3
Multivariable analysis for all patients. PORT: postoperative radiotherapy. SDH: sub-distribution hazard, HR: hazard ratio, CI: 95% confidence interval.

		Recurrence-free survival			MCC-related survival			Overall survival		
Characteristic		SDH	CI	P-value	SDH	CI	P-value	HR	CI	P-value
Sex	*Female*	1			1			1		
	Male	1.40	0.86-2.27	0.180	**2.21**	**1.07-4.56**	0.033	1.79	0.99-3.26	0.056
Age		1.00	0.98–1.03	0.970	1.00	0.96–1.04	0.980	1.01	0.99–1.05	0.252
Performance status										
	0	1			1			1		
	1	1.18	0.68–2.04	0.550	0.71	0.30–1.67	0.430	1.28	0.66–2.49	0.470
	2	0.74	0.32-1.70	0.480	0.75	0.27–2.09	0.580	**2.23**	**1.04–4.77**	**0.039**
	3	1.90	0.40-8.99	0.420	1.13	0.21–6.25	0.893	**3.36**	**1.03–10.94**	**0.044**
	Unknown	**5.33**	**2.02-14.09**	**<0.001**	**6.13**	**1.16–32.40**	**0.033**	**8.84**	**2.21–35.43**	**0.002**
Primary location										
	H&N	1			1			1		
	Trunk	1.18	0.59–2.33	0.650	2.19	0.92–5.20	0.075	**2.21**	**1.04–4.70**	**0.039**
	Extremity	0.69	0.38–1.26	0.230	1.03	0.45–2.38	0.930	0.78	0.39–1.58	0.496
	Unknown	0.44	0.18–1.08	0.074	0.33	0.06–1.69	0.180	0.42	0.13–1.38	0.153
Radical exision										
	No	1			1			1		
	Yes	0.68	0.28–1.63	0.390	0.53	0.11–2.50	0.420	0.83	0.29–2.43	0.741
Lymph-/angioinvasion	*No*	1			1			1		
	Yes	1.61	0.81–3.19	0.180	0.67	0.26–1.72	0.400	0.96	0.44–2.13	0.950
	Unknown	1.33	0.71–2.48	0.370	0.82	0.40–1.74	0.610	1.04	0.53–2.04	0.899
Stage										
	Path I/II	1			1			1		
	Clin I/II	**3.05**	**1.15–8.10**	**0.025**	**4.84**	**1.31–17.82**	**0.017**	**4.92**	**1.51–16.07**	**0.008**
	III	**6.24**	**2.68–14.54**	**<0.001**	**7.12**	**2.31–21.97**	**<0.001**	**7.81**	**2.60–23.50**	**<0.001**
PORT	*No*	1			1			1		
	Yes	**0.59**	**0.37–0.95**	**0.039**	0.83	0.43–1.62	0.580	**0.52**	**1.28–0.95**	**0.035**

Table 4
Multivariable analysis for stage III MCC patients. MCC: Merkel cell carcinoma, PORT: postoperative radiotherapy. SDH: sub-distribution hazard, HR: hazard ratio, CI: 95% confidence interval, H&N: head and neck.

		Recurrences			MCC-related mortality			Overall mortality		
Characteristic		SDH	CI	P-value	SDH	CI	P-value	HR	CI	P-value
Sex										
	Female	1			1			1		
	Male	1.48	0.62–3.56	0.380	1.60	0.30–2.21	0.490	1.19	0.46–3.09	0.718
Age		0.96	0.91–1.00	0.070	0.98	0.93–1.04	0.500	0.99	0.94–1.03	0.592
Performance status										
	0	1			1			1		
	1	1.30	0.54–3.12	0.560	1.10	0.28–4.03	0.890	1.25	0.46–3.42	0.663
	2	1.17	0.30–4.52	0.820	1.23	0.25–6.33	0.780	**5.64**	**1.80–17.64**	**0.003**
	*3**	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	
Primary location										
	H&N	1			1			1		
	Trunk	1.18	0.37–3.78	0.780	1.72	0.39–7.52	0.471	1.72	0.55–5.32	0.349
	Extremity	1.10	0.42–2.90	0.840	0.86	0.22–3.34	0.820	0.42	0.15–1.14	0.090
	Unknown	0.74	0.23–2.34	0.600	0.36	0.05–2.53	0.300	0.44	0.11–1.72	0.239
Radical excision										
	No	1			1			1		
	Yes	0.57	0.16–1.96	0.370	0.84	0.22–3.34	0.890	0.61	0.07–5.12	0.649
Lymph-/angioinvasion										
	No	1			1			1		
	Yes	0.78	0.31–1.95	0.600	0.36	0.07–1.88	0.220	0.66	0.18–2.48	0.543
	Unknown	**0.29**	**0.11–0.76**	**0.012**	0.35	0.07–1.61	0.180	0.45	0.13–1.56	0.207
Nodal status										
	1–3 nodes positive	1			1			1		
	≥4 nodes positive	1.56	0.61–4.02	0.350	**3.24**	**1.16–8.97**	**0.024**	2.77	0.93–8.27	0.067
	Unknown	0.49	0.15–1.57	0.230	0.57	0.09–3.66	0.550	1.96	0.49–7.87	0.343
Extracapsular extension	*No*	1			1			1		
	Yes	**4.09**	**1.43–11.65**	**0.012**	1.61	0.38–6.9	0.520	1.44	0.51–4.05	0.487
	Unknown	2.60	0.80–8.44	0.370	2.79	0.44–16.84	0.280	0.84	0.51–3.43	0.806
PORT	*No*	1			1			1		
	Yes	**0.45**	**0.20–0.98**	**0.044**	0.81	0.30–2.21	0.680	**0.37**	**0.15–0.91**	**0.031**

*Since this group only included one patient, results were left out of the analysis.

An important finding of our study is that c-I/II-MCC stage was associated with worse outcomes for all endpoints. This suggests that an important proportion of these, clinically node-negative patients, most likely had unidentified nodal disease. Analogous to the guideline discordance regarding PORT, deviations from protocol for SN biopsy or imaging were mostly due to patients' and clinicians' preference, comorbidities or patients' frailty. Similarly, in a study of patients with MCC of the head and neck, over half of the patients (52.2%) did not receive guideline-compliant regional lymph node evaluation. There, lymph-node evaluation was associated with improved OS in an inverse probability weighted multivariable regression [25]. These results underscore the need for SN biopsy in patients with c-I/II-MCC, since adequate staging leads to more appropriate treatment decision.

There are a number of limitations to the present study. First, although a fairly large group of patients for this rare disease were included, the cohort size was still relatively small. This might have led to our cohort being underpowered for assessment of treatment outcome associated with PORT. Nevertheless, we found distinctive differences between overall and MCC-specific mortality, which are unlikely to change with an increased sample size. Second, for some characteristics we encountered large proportions of missing values, such as lymph-/angioinvasion. For these, we were unable to draw conclusions regarding their association with prognosis, but by including missing values as 'unknown' categories in multivariable analysis, we were able to preserve statistical power and assess the value of other known prognostic characteristics such as nodal status or disease stage. Third, similar to nearly all studies involving patients with MCC, the retrospective observational nature is prone to bias. By performing PSM, we were able to create a cohort of treated and untreated patients that was balanced according to known characteristics associated with treatment decision. Of course, some relevant parameters, such as margin width, were missing in the majority of patients, and could not be included in the PSM analysis. Nonetheless, this inherently means that PSM analysis was conducted with knowledge highly similar to real clinical decisions, therefore we believe the analysis performed was an adequate representation of real-world practice. Interestingly, our matched cohort showed the same results as our unmatched cohort, suggesting that confounding by indication did not play a significant role in our cohort and our data for analysis of treatment outcome is robust.

The management of MCC has changed substantially over the past years: immune-checkpoint-inhibitors (ICI) have been introduced in the treatment of MCC and have changed the prognosis of patients tremendously [26–30]. ICI have been incorporated in the standard of care in the Netherlands since 2017, which means that a proportion of the patients included in this study did not yet have the opportunity to be treated with ICI [31]. Although this implies that the median survival for all patients nowadays might be longer than in this cohort, we do not expect any differences in the effect of PORT. Moreover, we have recently shown that there are no differences in response to ICI in patients with advanced MCC, with or without prior PORT [32]. The role of ICI in the adjuvant treatment of MCC is currently being explored prospectively in the ADMEC-O (NCT02196961), I-MAT (NCT04291885) and ADAM (NCT03271372) trials, including patients with or without prior PORT. The results from these studies will help further tailor the role for PORT in MCC.

In conclusion, this study is the first to directly address the probable influence of selection bias in the management and research of Merkel cell carcinoma. We have shown that PORT was associated with less recurrences in patients with stage III MCC, but not with improved MCC-specific mortality in patients with stage I-III MCC. Trends in overall survival benefit are likely to be caused by selection bias suggesting further refinement of criteria for PORT are warranted, for instance by taking life expectancy into account.

Funding

No funding was received for this study.

Data availability statement

Data are available upon reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors thank all the patients, the investigators of the study and supporting teams at each of the participating centers.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.11.017.

References

[1] Olsen CM, Pandeya N, Whiteman DC. International Increases in Merkel Cell Carcinoma Incidence Rates between 1997 and 2016. J Invest Dermatol 2021;141:2596–2601.e1.
[2] Schadendorf D, Lebbé C, zur Hausen A, Avril M-F, Hariharan S, Bharmal M, Becker JC. Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer 2017;71:53–69.
[3] Fondain M, Du Thanh A, Bessaoud F, Dereure O, Tretarre B, Guillot B. Epidemiological trends in Merkel cell carcinoma in southern France: a registry-based study. Br J Dermatol 2017;176:1379–81.
[4] Paulson KG, Park SY, Vandeven NA, Lachance K, Thomas H, Chapuis AG, et al. Merkel cell carcinoma: Current US incidence and projected increases based on changing demographics. J Am Acad Dermatol 2018;78:457–463.e2.
[5] Schadendorf D, Lebbé C, Zur Hausen A, Avril MF, Hariharan S, Bharmal M, et al. Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer 2017;71:53–69.
[6] 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, Annals of surgical oncology 23(11) (2016) 3564-3571.
[7] van Veenendaal LM, van Akkooi ACJ, Verhoef C, Grunhagen DJ, Klop WMC, Valk GD, et al. Merkel cell carcinoma: Clinical outcome and prognostic factors in 351 patients. J Surg Oncol 2018;117:1768–75.
[8] Bleicher J, Asare EA, Flores S, Bowles TL, Bowen GM, Hyngstrom JR. Oncologic outcomes of patients with Merkel Cell Carcinoma (MCC): A multi-institutional cohort study. Am J Surg 2021;221:844–9.
[9] C.D. Schmults, R.B. Blitzblau, S.B. Aasi, M. Alam, J.S. Andersen, J. Bordeaux, et al., National Comprehensive Cancer Network Guidelines for Merkel Cell Carcinoma, Version 2, 2019, 2019.
[10] Andruska N, Mahapatra L, Brenneman RJ, Rich JT, Baumann BC, Compton L, et al. Reduced wide local excision margins are associated with increased risk of relapse and death from Merkel cell carcinoma. Ann Surg Oncol 2021;28:3312–9.
[11] Wright GP, Holtzman MP. Surgical resection improves median overall survival with marginal improvement in long-term survival when compared with definitive radiotherapy in Merkel cell carcinoma: A propensity score matched analysis of the National Cancer Database. Am J Surg 2018;215:384–7.
[12] Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant Local Irradiation for Merkel Cell Carcinoma. Arch Dermatol 2006;142:693–700.
[13] Bhatia S, Storer BE, Iyer JG, Moshiri A, Parvathaneni U, Byrd D, et al. Adjuvant radiation therapy and chemotherapy in merkel cell carcinoma: Survival analyses of 6908 cases from the national cancer data base. J Natl Cancer Inst 2016;108.
[14] Tseng YD, Apisarnthanarax S, Liao JJ, Bhatia S, Nghiem PT, Parvathaneni U. Factors influencing radiation treatment recommendations in early-stage Merkel cell carcinoma: a survey of US-based radiation oncologists. Expert Rev Anticancer Ther 2017;17:281–7.
[15] Wong WG, Stahl K, Olecki EJ, Holguin RP, Pameijer C, Shen C. Survival Benefit of Guideline-Concordant Postoperative Radiation for Local Merkel Cell Carcinoma. The Journal of surgical research 2021;266:168–79.
[16] Harounian JA, Molin N, Galloway TJ, Ridge D, Bauman J, Farma J, et al. Effect of sentinel lymph node biopsy and LVI on Merkel cell carcinoma prognosis and treatment. The Laryngoscope 2021;131:E828–35.

[17] Petrelli F, Ghidini A, Torchio M, Prinzi N, Trevisan F, Dallera P, et al. Adjuvant radiotherapy for Merkel cell carcinoma: A systematic review and meta-analysis. Radiother Oncol 2019;134:211–9.
[18] Kim JA, Choi AH. Effect of radiation therapy on survival in patients with resected Merkel cell carcinoma: a propensity score surveillance, epidemiology, and end results database analysis. JAMA Dermatol 2013;149:831–8.
[19] Yin X, She H, Martin Kasyanju Carrero L, Ma W, Zhou B. Nomogram prediction for the overall survival and cancer-specific survival of patients diagnosed with Merkel cell carcinoma. Ann. Transl. Med. 2021;9:286.
[20] Xia Y, Cao D, Zhao J, Zhu B, Xie J. Clinical features and prognosis of Merkel cell carcinoma in elderly patients. Med Sci Monitor 2020;26:e924570.
[21] Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials - greater precision but with greater uncertainty? JAMA 2003;289:2554–9.
[22] Lauer MS, Topol EJ. Clinical trials—multiple treatments, multiple end points, and multiple lessons. JAMA 2003;289:2575–7.
[23] Montori VM, Permanyer-Miralda G, Ferreira-González I, Busse JW, Pacheco-Huergo V, Bryant D, et al. Validity of composite end points in clinical trials. BMJ 2005;330:594–6.
[24] Hernan MA, Schisterman EF, Hernandez-Diaz S. Invited commentary: composite outcomes as an attempt to escape from selection bias and related paradoxes. Am J Epidemiol 2014;179:368–70.
[25] Jacobs D, Olino K, Park HS, Clune J, Cheraghlou S, Girardi M, et al. Primary treatment selection for clinically node-negative Merkel cell carcinoma of the head and neck. Otolaryngology–Head Neck Surgery 2021;164:1214–21.
[26] D'Angelo SP, Russell J, Lebbé Céleste, Chmielowski B, Gambichler T, Grob J-J, et al. Efficacy and safety of first-line avelumab treatment in patients with stage IV metastatic merkel cell carcinoma: A preplanned interim analysis of a clinical trial. JAMA Oncol 2018;4:e180077. https://doi.org/10.1001/jamaoncol.2018.0077.
[27] Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016;17:1374–85.
[28] Nghiem FT, Bhatia S, Lipson EJ. Durable tumor regression and overall survival in patients with advanced merkel cell carcinoma receiving pembrolizumab as first-line therapy. J Clin Oncol 2019;37:693–702.
[29] Paulson KG, Bhatia S. Advances in immunotherapy for metastatic merkel cell carcinoma: A clinician's guide. J Natl Compreh Cancer Network JNCCN 2018;16:782–90.
[30] Garcia-Carbonero R, Marquez-Rodas I, de la Cruz-Merino L, Martinez-Trufero J, Cabrera MA, Piulats JM, et al. Recent therapeutic advances and change in treatment paradigm of patients with merkel cell carcinoma. Oncologist 2019;24:1375–83.
[31] EMA, Summary Of Opinion - Initial Authorisation of Avelumab, Committee for Medicinal Products for Human Use (EMA/CHMP/426201/2017) (2017).
[32] Levy S, Aarts MJB, Eskens FALM, Keymeulen KBMI, Been LB, Grünhagen D, et al. Avelumab for advanced Merkel cell carcinoma in the Netherlands; a real-world cohort. J ImmunoTherapy Cancer 2020;8:e001076. https://doi.org/10.1136/jitc-2020-001076.